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Update of Comparative Effectiveness of Lipid-Modifying Agents

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Statement of Funding and Purpose

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The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://www.effectivehealth care.ahrq.gov/reference/purpose.cfm

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (http://www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Health care Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

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The investigators deeply appreciate the considerable support, commitment, and contributions of the EPC team staff at <NAME>. We express our gratitude to the following individuals for their contributions to this project: <NAME, degrees>

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Structured Abstract

Objective: To compare the benefits and harms of combination of statin and other lipid-modifying medication to intensification of statin monotherapy.

Data Sources: Reports of studies from MEDLINE®, Embase®, Cochrane Central Register of Controlled Trials (CENTRAL) from May 2008 to January 2013.

Review Methods: Paired investigators independently screened search results to assess eligibility. Investigators abstracted data sequentially and assessed risk of bias independently. Investigators graded the strength of evidence (SOE) as a group.

Results: All evidence for clinical outcomes (mortality, acute coronary events, and revasculartization procedures) were graded as insufficient across all potency comparisons for all combination therapy regimens.
Bile Acid Sequestrants (BAS): Moderate SOE from 4 trials found that a low potency statin combined with a BAS lowered LDL-c up to 14 percent more than mid potency statin monotherapy.
Ezetimibe: Moderate SOE from 12 trials favors mid potency statin with ezetimibe for lowering LDL-c as compared to high potency statin monotherapy among general populations. Low SOE from 10 trials favors mid potency statin with ezetimibe for raising HDL-c as compared to high potency statin monotherapy. However, there is high SOE from 3 trials that favors high potency statin monotherapy in terms of lower rates of serious adverse effects as compared to mid potency statin with ezetimibe.
Fibrates: Moderate SOE from 6 trials found that high potency statin monotherapy lowered LDL-c up to 15 percent more than mid potency statin with fibrate. However, mid potency statin with fibrate raised HDL-c up to 10 percent more than high potency statin monotherapy.
Niacin: Low SOE from 4 trials found that high potency statin monotherapy lowers LDL-c up to 12 percent more than mid potency statin with niacin. However, mid potency statin with niacin raises HDL-c up to 16 percent more than high potency statin monotherapy. Moderate SOE from 3 trials found that low potency statin with niacin raises HDL-c up to 27 percent more than mid potency statin monotherapy.
Omega-3 Fatty Acids: Only two trials evaluated this comparison, and therefore, graded SOE as insufficient.

Conclusions: Combination of statin with ezetimibe or bile acid sequestrant lowered LDL-c better than intensification of statin monotherapy, while intensification of statin monotherapy was preferable in reducing LDL-c when considering combination therapy with niacin or fibrate. Unfortunately, few studies addressed the question of which approach produces better clinical outcomes. Additional studies evaluating long-term clinical benefits and harms are needed to better inform clinical decisionmaking, patient choice, and clinical practice guidelines.

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Executive Summary

Background

Cardiovascular disease (CVD) includes conditions such as coronary heart disease, stroke, heart failure, arrhythmia, heart valve disease, congenital heart disease, and hypertension. The American Heart Association has estimated that CVD affects 83.6 million individuals, contributes to 32.3 percent of deaths, and is a leading cause of disability.[1] Atherosclerosis plays a major role in the development of atherosclerotic CVD, which is a subset of CVD that includes coronary heart disease (CHD), cerebrovascular disease, and peripheral artery disease. The American Heart Association estimates that atherosclerotic CVD affects 15.4 million Americans.[1] CHD, which includes coronary artery disease (CAD), myocardial infarction (MI), unstable angina (UA), and heart failure, is a leading cause of death for both men and women in the U.S.[2] By 2030, the prevalence of CHD will rise by 16.6 percent and result in over $106 billion in direct healthcare costs.[3]

Abnormal lipoprotein metabolism predisposes individuals to atherosclerosis, especially increased concentrations of apo B-100-containing low-density lipoprotein (LDL-c). Due to the consistent and robust association of higher LDL-c levels with atherosclerotic CVD across experimental and epidemiologic studies,[4,5]therapeutic strategies to decrease risk have focused on LDL-c reduction as the primary goal. In contrast to LDL-c, high-density lipoprotein (HDL-c) has a protective role against atherosclerotic CVD. Epidemiologic studies have demonstrated an inverse association between HDL-c and CVD, where low HDL-c levels are independent predictors of CHD.[6,7]

The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III provides guidelines on when to initiate lipid-lowering therapy as well as recommended LDL-c targets for optimal CHD risk reduction.[8,9] ATP III defined the highest risk individuals as those with established CHD, other clinical atherosclerotic CVD, or multiple risk factors for atherosclerotic CVD. These high-risk individuals have a 10-year CHD risk greater than 20 percent, and their LDL-c target is less than 100 mg/dL (optional goal <70 mg/dL). Moderate risk patients are those with 2 or more risk factors and a 10-year CHD risk less than 20 percent. The LDL target for moderate risk patients is less than 130 mg/dL, but the threshold for starting drug therapy depends on their CHD risk level. For moderate risk patients with a 10-year CHD risk of 10-20 percent, providers should consider drug therapy if the LDL-c is above 130 mg/dL. For moderate risk patients with a 10-year CHD risk less than 10 percent, drug therapy does not need to be considered until the LDL-c reaches 160 mg/dL. Later in 2013, many anticipate an update of these guidelines (ATP IV) will be released. Based upon the revised recommendations from organizations such as the American Diabetes Association (ADA) and the American College of Cardiology Foundation (ACCF), some have speculated that ATP IV may expand focus of lipid lowering beyond LDL-c with greater emphasis on non-HDL-c and ApoB.[10] However, other experts have advocated that ATP IV should not recommend LDL-c targets and rather support tailored treatment as a simpler, safer, and more effective option.[11]

In addition to the current uncertainty regarding future guideline recommendations, additional controversy surrounds lipid modifying medication practices among patients who require intensive therapy. While 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or “statins” are the most widely prescribed lipid-lowering agents and are often used as monotherapy; alternatively, statins can be combined with another medication such as bile acid sequestrants, cholesterol absorption inhibitor, fibric acids, nicotinic acid, and omega-3 fatty acids. Many trials comparing these combination regimens to statin monotherapy such as

ENHANCE, AIM-HIGH, and ACCORD-lipid have demonstrated that combination therapy can lead to superior lipid outcomes, but fails reduce measure of atherosclerosis or lead to decreased rates of cardiovascular death, MI, revascularization, or stroke.[12-14] In addition, combination regimens may worsen clinical outcomes, such as the potential worsening of atherosclerosis reported with the combination of statin and ezetimibe.[15]

In 2009, the Agency for Healthcare Research and Quality (AHRQ) released an evidence report examining these lipid-modifying agents.[16,17] However, the authors found insufficient evidence to determine whether combination therapy held benefit over monotherapy. To provide additional guidance to clinicians treating patients with moderate or high CHD risk, this update review addresses long-term benefits and rates of serious adverse events (SAEs) associated with co-administration of different lipid-modifying agents compared with higher potency statin monotherapy among patients at moderate and high CHD risk, defined as a 10-year CHD risk greater than 10 percent or LDL greater than 160 mg/dL, as these patients may require intensive lipid modifying therapy to achieve their LDL goals.

Scope and Key Questions

We aimed to compare the effectiveness, safety, and tolerability of combination of statin and other lipid-modifying medication to intensification of statin monotherapy. Our scope was limited to comparing combination of statin with other lipid-modifying medication to intensification of statin monotherapy as proposed in the key questions. While several trials have shown that non-statin monotherapy may not improve clinical outcomes, we did not include non-statin monotherapy as a comparison group because it was outside the scope of our key questions for this report.We aimed to answer the questions below by reviewing trials of adults that compared a higher potency of statin monotherapy to a lower potency statin in combination with another agent (bile acid sequestrant, ezetimibe, fibrate, niacin, or omega-3 fatty acid).

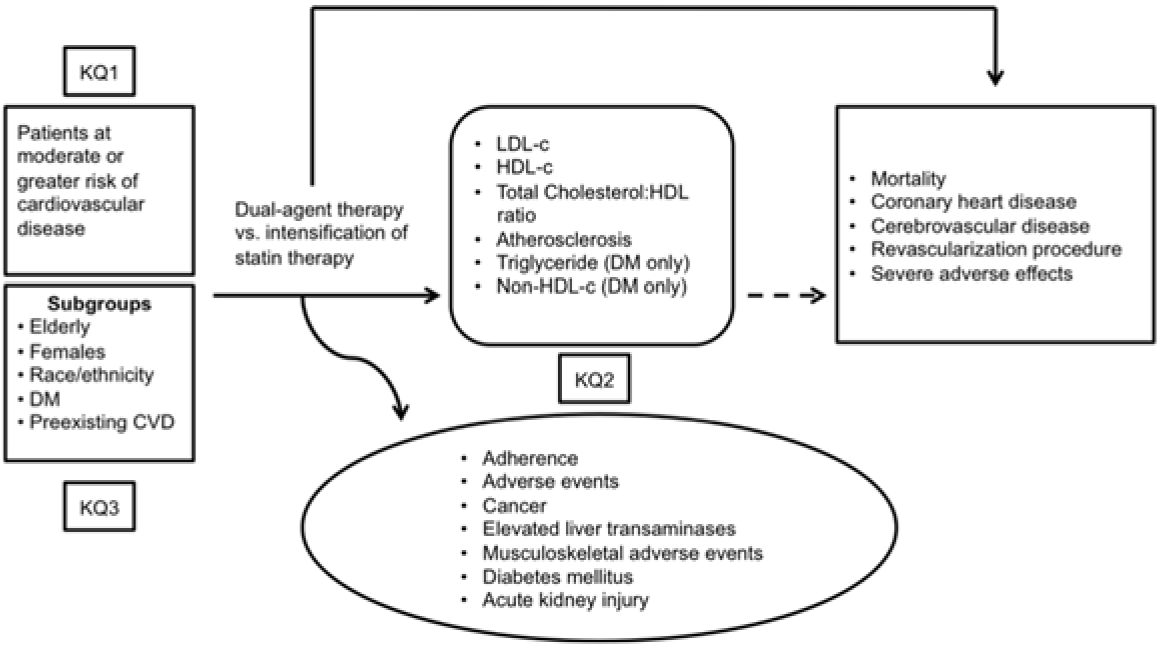
The specific Key Questions (KQ) are:

KQ 1: For patients who require intensive lipid-modifying therapy, what are the comparative long-term benefits and rates of serious adverse events of co-administration of different lipid-modifying agents (i.e., a statin plus another lipid-modifying agent) compared with higher dose statin monotherapy?

KQ 2: Do these regimens differ in reaching LDL targets (or other surrogate markers), short-term side effects, tolerability, and/or adherence?

KQ 3: Compared with higher dose statins and to one another, do combination regimens differ in benefits and harms within subgroups of patients?

Figure 1. Analytic Framework for Comparative Effectiveness of Lipid-Modifying Agents



KQ= key question, CVD= cardiovascular disease, DM= diabetes mellitus, HDL= high density lipoprotein; LDL= low density lipoprotein

Methods

Search Strategy, Study Selection and Data Abstraction

We searched the following databases for primary studies: MEDLINE,® Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) from May 2008 through January 2013. We also reviewed relevant review articles. In addition, we requested and reviewed Scientific Information Packets (SIPs) provided by the pharmaceutical manufacturers.

Abstract and full-text screening was performed by two independent reviewers using prespecified eligibility criteria (Table 1). All articles included in the prior review were reviewed during the full-text screen. Conflicts were resolved by consensus adjudication.

Data abstraction was conducted with a senior reviewer (faculty level project investigator) abstracting data from articles while having access to the first reviewer's data abstraction. Differences in opinion were resolved through consensus adjudication and, for difficult cases, during team meetings.

Table 1. Study inclusion and exclusion criteria

Population and condition of interest	Adults with moderate (10-year CHD risk 10-20 percent or LDL≥160 mg/dL) or high (10-year CHD risk≥20 percent or LDL≥190 mg/dL) cardiovascular disease risk *Excluded* studies if they included only adults with low cardiovascular disease risk (CHD risk<10 percent or LDL<160 mg/dL) *Excluded* studies that included only patients with homozygous familial hypercholesterolemia (FH)
Interventions and approaches	Studies must have evaluated a combination regimen of interest Included studies of bile acid sequestrants + statin Included studies of ezetimibe + statin Included studies of fibrates + statin Included studies of niacin + statin Included studies of omega-3 fatty acids + statin *Excluded* studies of lifestyle modifications *Excluded* studies of drugs approved only from the treatment of homozygous FH *Excluded* studies of drugs not approved by the FDA or investigational drug *Excluded* studies of prepackaged medications that contained non lipid-lowering medications
Comparisons of interest	Included comparisons of higher potency statin monotherapy *Excluded* studies if a study statin monotherapy was of the same or lower potency than combination arm *Excluded* studies if there was no comparison or only placebo comparison.
Outcomes and Timing	Clinical outcomes including mortality, cardiovascular events, cerebrovascular events, revascularization procedures at any time point Surrogate outcomes including LDL-c, HDL-c, TC:HDL-c ratio, NCEP ATP IIL LDL-c target attainment, measures of atherosclerosis at any time point. Triglycerides and non-HDL-c in diabetes subgroup. Adherence and harms outcomes including adherence, serious adverse events, withdrawal due to adverse events, cancer, elevated liver transaminases, adverse musculoskeletal adverse events, diabetes mellitus, acute kidney injury at any time point
Type of study	Included studies with any sample size that met all other criteria. Included studies from the prior report that met all other criteria. Included randomized controlled trials () Included non-randomized extension of clinical trial over 24 weeks duration (clinical outcomes, SAE and harms only), and Included FDA reports (SAE and harms only) *Excluded* studies with other observational designs. *Excluded* studies with no original data (reviews, editorials, comments, letters, modeling only studies). *Excluded* studies published only as abstracts. *Excluded* qualitative studies. *Excluded* crossover trials with fewer than 4 weeks washout and/or lacking paired observation, within person differences, or pre-crossover data. *Excluded* non-English publications.

CHD= coronary heart disease; FH =familial hypercholesterolemia; FDA= Food and Drug Administration; HDL= high density lipoprotein; LDL= low density lipoprotein; RCT= randomized controlled trial; SAE= serious adverse event; TC= total cholesterol;

Risk of Bias Assessment

Risk of bias was assessed independently by two reviewers using the Cochrane Collaboration's tool (Appendix F). For studies included from the prior review, we used the prior quality assessments reported in that report which used the Jadad Score.

Data Synthesis

We compared lower potency statins in combination therapy to higher potency statin monotherapy, which enabled us to synthesize data across statin type and statin dose. We used specific criteria to determine statin potency (Table 2).

Table 2. List of Different Dosing of Specific Statins Based on Potency to Reduce LDL-c

Statin	Atorvastatin (mg/day)	Fluvastatin (mg/day)	Fluvasatin XL (mg/day)	Lovastatin (mg/day)	Pitavastatin (mg/day)	Pravastatin (mg/day)	Rosuvastatin (mg/day)	Simvastatin (mg/day)
Low Potency (<30 percent LDL reduction)	5	20 and/or 40	--	5 and/or 10 and/or 20	1	10 and/or 20 and/or 40	--	10
Mid Potency (30-40 percent LDL reduction)	10	80	80	40 and/or 80	2 and/or 4	80	5 and/or 10	20
High Potency (>40 percent LDL reduction)	20 and/or 40 and/or 80	--	--	--	--	--	20 and/or 40	40 and/or 80*

*Studies that use simvastatin 80mg in statin naïve patients will be excluded.

We calculated and displayed the mean differences with 95 percent confidence intervals (CI) for the individual studies grouped by combination therapy agent, statin potency, and population for all comparisons. We considered meta-analysis where there were three or more similar studies. We report qualitative synthesis of data for most outcomes because of the lack of outcomes meeting our criteria for meta-analysis and significant heterogeneity detected when meta-analyses were conducted (I^2>50%).

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Strength of the Body of Evidence

We graded the quantity, quality and consistency of the evidence for the following outcomes: mortality, acute coronary events, revascularization procedures, serious adverse events, LDL-c, and HDL-c. We used an evidence grading scheme recommended by the Methods Guide for Conducting Comparative Effectiveness Reviews.[18] We created evidence grades for each comparison and outcome by combination agent, statin potency, and population. We used four domains to yield a final evidence grade: risk of bias, consistency, directness and precision.

The final evidence grades were: (1) "high" grade (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of the effect); (2) "moderate" grade (indicating moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of the effect and may change the estimate); (3) "low" grade (indicating low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate); and (4) "insufficient" grade (no evidence identified). A comparison-outcome pair with high strength of evidence was one with low risk of bias, directness, consistency, and precision. Moderate strength of evidence indicated a high risk of bias was noted or that *two* of the following were observed: a moderate risk of bias, inconsistency, indirectness or imprecision. Low strength of evidence indicated a high risk of bias and *two* or more of the following or a moderate risk of bias and three of the following: inconsistency, indirectness and imprecision.

Investigators writing each section completed the strength of evidence grading which was then reviewed by the team.

Applicability

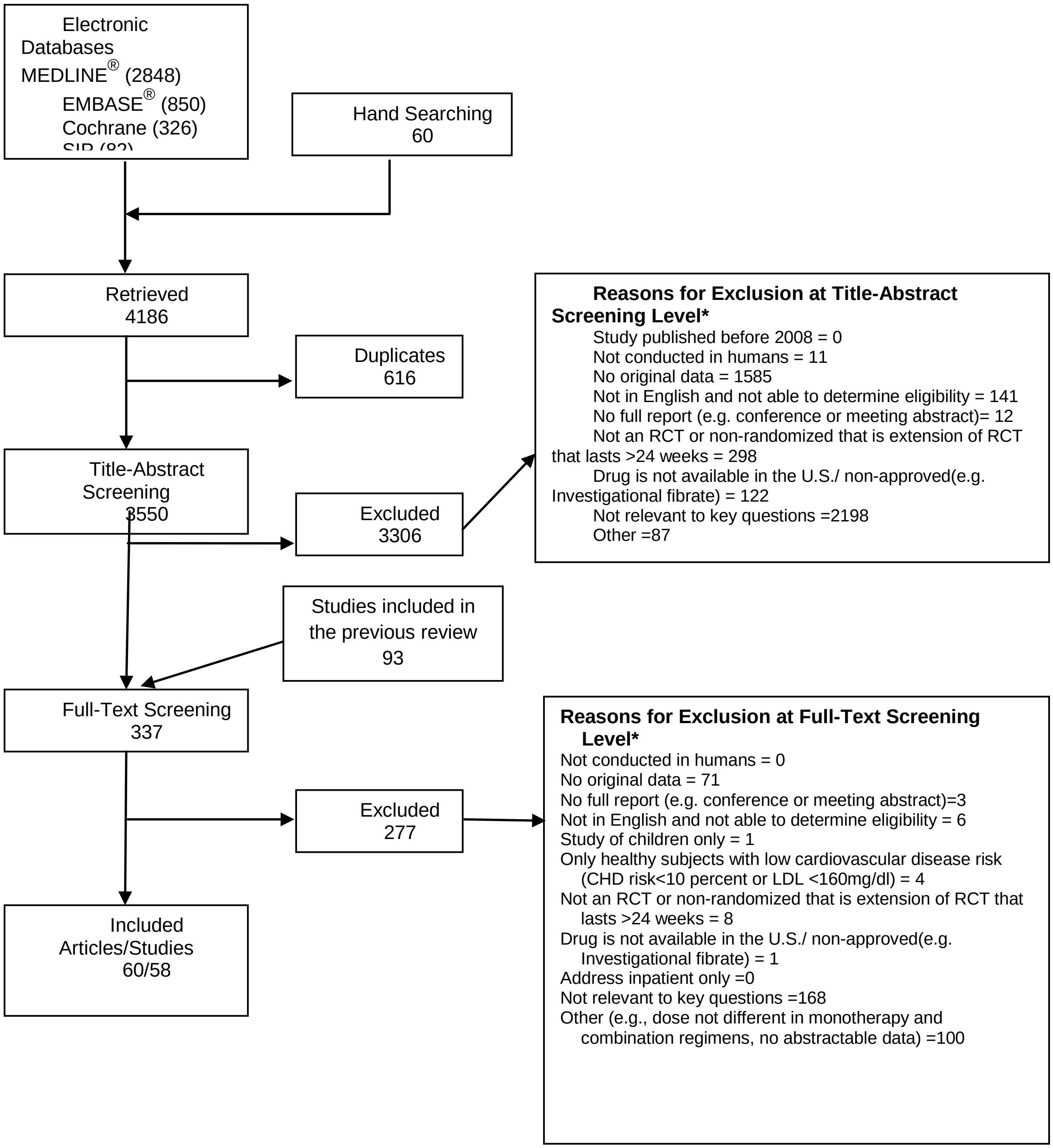
We describe the applicability of studies in terms of the degree to which the study population, interventions, outcomes, and settings were relevant to individuals at high CHD risk requiring aggressive lipid-modifying therapy and features that may affect the effectiveness of the intervention.

Results

Results of Literature Searches

Figure 2 summarizes the search results. The literature search identified 4,084 unique citations. During the title and abstract screening we excluded 3,306 citations; during the article screening we excluded 277 citations (Appendix D). Fifty-eight studies, reported in 60 articles, were included. All trials were randomized controlled trials.

Figure 2. Summary of search (number of articles)



* Total exceeds the number of citations in the exclusion box, because citations could be excluded for more than one reason

Overview of included trials by potency and agent

The strength of evidence was variable across comparisons evaluating the effectiveness and safety of combination therapy to intensification of statin monotherapy. Only one comparison had high strength of evidence for serious adverse events and nine comparisons had moderate strength of evidence for LDL-c and HDL-c outcomes. However, all other comparisons and outcomes had low or insufficient evidence. All evidence for the clinical outcomes of mortality, acute coronary events, and revascularization procedures were graded as insufficient across all potency comparisons for all combination therapy regimens.

The interventions and approaches that effectively lowered LDL-c or raised HDL-c are described by combination therapy regimen below. The strength of evidence for the body of evidence is provided in Table 3 for general populations and Table 4 for subgroups.

Table 3. Summary of the strength of evidence for general populations

	Potency Comparisons (combination therapy vs. monotherapy)	Mortality	Acute Coronary Events	Revascularization Procedures	Serious Adverse Events	LDL-c	HDL-c
Bile Acid Sequestrant	Low potency vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Mid potency vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Low potency vs mid potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	**Moderate with combination therapy favored**	Insufficient
Ezetimibe	Low potency vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	**Low with combination therapy favored**	**Low with combination therapy favored**
	Mid potency vs high potency monotherapy	Insufficient	Insufficient	Insufficient	**High with monotherapy favored**	**Moderate with combination therapy favored**	**Low with combination therapy favored**
	Low potency vs mid potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	**Moderate with combination therapy favored**	**Low with combination therapy favored**
Fibrates	Low potency vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Mid potency vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	**Moderate with monotherapy favored**	**Moderate with combination therapy favored**
	Low potency vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Niacin	Low potency vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient

	Potency Comparisons (combination therapy vs. monotherapy)	Mortality	Acute Coronary Events	Revascularization Procedures	Serious Adverse Events	LDL-c	HDL-c
	Mid potency vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	**Low with monotherapy favored**	**Low with combination therapy favored**
	Low potency vs mid potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	**Moderate with combination therapy favored**
Omega-3 Fatty Acid	Low potency vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Mid potency vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Low potency vs mid potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient

HDL=high density lipoprotein; LDL= low density lipoprotein

Table 4. Summary of the strength of evidence for <u>subgroups</u>

Subgroup	Combination Agent	Potency Comparisons (combination therapy vs. monotherapy)	Mortality	Acute Coronary Events	Revascularization Procedures	Serious Adverse Events	LDL-c	HDL-c
Preexisting CHD	Ezetimibe	Low potency vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
		Mid potency vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	**Moderate with combination therapy favored**	**Low with combination therapy favored**
		Low potency vs mid potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Fibrates	Mid potency vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Diabetes	Ezetimibe	Low potency vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
		Mid potency vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	**Moderate with combination therapy favored**	**Moderate with combination therapy favored**
		Low potency vs mid potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Fibrates	Low potency vs mid potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient

CHD= coronary heart disease; LDL= low density lipoprotein

Combination Therapy with Bile Acid Sequestrant and Statin versus Intensification of Statin Monotherapy

Six randomized trials (410 participants) were identified. Four trials compared low potency statin in combination with a bile acid sequestrant to mid potency statin monotherapy (288 participants). Low potency statin in combination with a bile acid sequestrant lowers LDL-c up to 14 percent more than mid potency statin monotherapy (SOE: moderate). There was insufficient evidence to evaluate LDL-c outcomes for other potency comparisons and insufficient evidence to compare HDL-c outcomes at any statin potency.

We found insufficient evidence to compare combined lipid-modifying therapy with a bile acid sequestrant and statin to intensification of statin monotherapy on the rates of serious adverse events, regardless of statin potency. No study reported on the comparative effectiveness of bile acid sequestrant plus statin on benefits or harms as compared to intensification of statin monotherapy among subgroups.

Combination Therapy with Ezetimibe and Statin versus Intensification of Statin Monotherapy

Thirty-eight randomized trials (10,955 participants) were identified, which primarily reported on surrogate outcomes such as LDL-c and HDL-c. Twelve trials compared low potency statin in combination with ezetimibe to high potency statin monotherapy (1,571 participants). Among general populations, low potency statin in combination with ezetimibe more effectively lowers LDL-c and raises HDL-c as compared to high potency statin monotherapy (SOE: low).

Twelve trials compared mid potency statin in combination with ezetimibe to high potency statin monotherapy in general populations (5,991 participants). Mid potency statin combined with ezetimibe more effectively lowers LDL-c and raises HDL-c as compared to high potency statin monotherapy among general populations (SOE: moderate and low, respectively). However, high potency statin monotherapy produces fewer serious adverse events than combination of mid potency statin with ezetimibe (SOE: high).

Seven trials compared low potency statin in combination with ezetimibe to mid potency statin monotherapy (1,195 participants). Low potency statin in combination with ezetimibe more effectively lowers LDL-c and raises HDL-c as compared to mid potency statin monotherapy (SOE: moderate and low, respectively).

Ten trials compared mid potency statin in combination with ezetimibe to high potency statin monotherapy among patients with preexisting coronary heart disease (1,050 participants) and three trials among patients with diabetes (1,581 participants). Mid potency statin combined with ezetimibe more effectively lowers LDL-c and raises HDL-c as compared to high potency statin monotherapy among patients with coronary heart disease (SOE: moderate and low, respectively). Mid potency statin combined with ezetimibe more effectively lowers LDL-c and raises HDL-c as compared to high potency statin monotherapy among patients with diabetes (SOE: moderate).

Combination Therapy with Fibrate and Statin versus Intensification of Statin Monotherapy

Eight randomized trials (1,824 participants) were identified. Six trials compared mid potency statin in combination with fibrate to high potency statin monotherapy (1,585 participants). High potency statin monotherapy lowers LDL-c up to 15 percent more than mid potency statin in combination with fibrate (SOE: moderate). However, mid potency statin in combination with fibrate raises HDL-c up to 10% more than high potency statin monotherapy (SOE: moderate). We found insufficient evidence to compare combined lipid-modifying therapy with a fibrate and statin to intensification of statin monotherapy on the rates of serious adverse events, regardless of statin potency.

Combination Therapy with Niacin and Statin versus Intensification of Statin Monotherapy

Seven randomized trials (876 participants) were identified. Four trials compared mid potency statin in combination with niacin to high potency statin monotherapy (629 participants). High potency statin monotherapy lowers LDL-c up to 12 percent more than mid potency statin in combination with niacin (SOE: low). However, mid potency statin in combination with niacin raises HDL-c 11 percent to 26 percent more than high potency statin monotherapy (SOE: low). Three trials compared low potency statin in combination with niacin to mid potency statin monotherapy (247 participants). We found inconsistent effects on lowering LDL-c when comparing low potency statin in combination with niacin and mid potency statin monotherapy. However, low potency statin in combination with niacin raised HDL-c 15 percent to 27 percent more than mid potency statin monotherapy (SOE: moderate).

We found insufficient evidence to compare combined lipid-modifying therapy with niacin and statin to intensification of statin monotherapy on the rates of serious adverse events, regardless of statin potency. No study reported on the comparative effectiveness of niacin plus statin on benefits or harms as compared to intensification of statin monotherapy among subgroups.

Combination Therapy with Omega-3 Fatty Acid and Statin versus Intensification of Statin Monotherapy

Two randomized trials (99 participants) were identified; both compared a mid potency statin in combination with omega-3 fatty acid to high potency statin monotherapy. There is insufficient evidence to compare the benefits of combined lipid-modifying therapy with an omega-3 fatty acid and statin to intensification of statin monotherapy on LDL-c, HDL-c and serious adverse events, regardless of statin potency.

Discussion

Key Findings

The evidence suggests that some combination therapy regimens may confer benefits with respect to lowering LDL-c including bile acid sequestrants and ezetimibe. In contrast, intensification of statin monotherapy provided benefits or showed little difference with respect to LDL-c lowering in comparison to combination therapy with fibrates or niacin. LDL-c is an important factor in the development of atherosclerotic cardiovascular disease and higher levels of LDL-c have been associated with greater risk of this disease.[4,5] However, there is insufficient evidence to address whether these LDL-c lowering benefits achieved with these medications translate into decreased rates of atherosclerotic cardiovascular disease. Prior trials comparing combination regimens to statin monotherapy such as ENHANCE, AIM-HIGH, and ACCORD-lipid have demonstrated that combination therapy can lead to superior lipid outcomes, but fail to reduce clinical outcomes such as cardiovascular death, MI, revascularization, or stroke.[12-14] Most trials included in this report were of relatively short duration (<3 months). In this limited timeframe, investigators are unlikely to capture any changes in a chronic condition like atherosclerotic cardiovascular disease, which typically develops and progresses over a number of years. The strength of evidence for all observed comparisons in general populations is provided in Table 3 and in subgroups in Table 4. Several comparisons were graded as having moderate strength of evidence. Most comparisons have low or insufficient evidence. These results may help aid individual decision-making and patient management. Overall, the findings suggest that healthcare providers should consider tailoring the lipid-modifying regimen based on individual patient needs and concerns for adverse events, which has also been advocated by some other experts in this field.[11]

Applicability

Many trials that met our inclusion criteria were implemented in populations of hyperlipidemic patients, and most were designed to evaluate effects on lipid measures and short-term harms. The results of most trials generalize to patients with hyperlipidemia uncomplicated by other major co-morbid conditions. Interestingly, we identified fewer trials that were conducted among high CHD risk patients such as those with diabetes or preexisting cardiovascular disease. These patients could benefit from improvement in their lipid profiles and are the most likely to be receiving more aggressive lipid-modifying regimens in clinical practice.

Most trials we identified were of relatively short duration, despite the fact that these medications are currently used in clinical practice as chronic, long-term medications. In addition, losses to followup and medication adherence by intervention arm were often not reported in trials, which may bias our results. While our findings may suggest that one therapeutic option provides a benefit over another, we cannot comment on the tolerability of or persistence to the regimen given the lack of data and short trial duration. Additional long-term trials are needed to compare the tolerability, side effects, and harms with prolonged use of these medications.

Limitations of the Review Process and Evidence Base

The strength of evidence was insufficient for many comparison outcome relationships because of a paucity of studies. We were unable to grade any strength of evidence as high, despite numerous trials within some comparisons. Trials were frequently downgraded in risk of bias assessment for lack of blinding by participant and study personnel (performance bias), for not reporting the blinding of outcome assessors (detection bias), or for not accounting for losses to followup or handling of incomplete data (attrition bias). Few studies reported variance estimates for the between group differences in any outcomes over time. In some instances, the studies did not report a mean difference or point estimate stating there was no significant difference between the groups. In addition, some studies did not report an intention-to-treat analysis and others did not specify the number analyzed in each arm. All of these factors limited our ability to conduct meta-analyses. Where we conducted meta-analysis, substantial heterogeneity was present in most cases.

Few trials specifically targeted patients at highest CHD risk. Populations such as patients with diabetes or prior atherosclerotic cardiovascular disease represent a great clinical challenge with respect to what their lipid treatment targets should be and how to accomplish these goals. Second, many trials that we reviewed either compared a therapeutic regimen to placebo or compared combination and monotherapy arms of the same statin potency. Neither of these study designs enabled us to answer the questions proposed, and were therefore excluded. Third, many studies either did not evaluate or were of insufficient duration to adequately assess long-term clinical outcomes including mortality, acute coronary events, and revascularization procedures; and therefore, this report focuses primarily on LDL-c and HDL-c outcomes. While many trials focused on examining these outcomes, the clinical field may be moving towards emphasizing additional lipid measures such as non-HDL-c and ApoB as new targets. In addition, the ADA and ACCF have released guidelines that suggests a new LDL-c goal <70 mg/dL for the highest risk patients, rather than a goal of <100 mg/dL in ATP III.[10] If upcoming release of ATP IV makes similar recommendations, then this report may not adequately compare the effectiveness of combination therapy regimens to intensification of statin monotherpay in terms of achieving these new goals.

Strengths of the Evidence Base

Many studies included populations of at least moderate CHD risk for whom the decision between combination therapy and intensification of statin monotherapy is likely a clinical conundrum for both patients and healthcare providers.

Future Research Needs

We suggest that most comparisons and outcomes that have low or insufficient evidence are future research needs. In order to answer whether there are long-term benefits with respect to mortality, acute coronary events, and revascularization procedures, future investigators need to make these endpoints the primary outcomes of their trials and ensure that trials are of sufficient duration to actually capture these events (at least 12 months or preferably longer). Recent trials such as ENHANCE, ACCORD, and AIM-HIGH have failed to show any additional clinical benefit of combination therapy as compared to statin monotherapy.[12-14] While the forthcoming IMPROVE-IT trial may be able to clarify whether ezetimibe + simvastatin is superior to simvastatin alone with respect to cardiovascular deaths, MI or strokes, this trial uses equivalent doses of simvastatin in the combination and monotherapy arms.[19] This trial will not inform decisions about the effect of intensification of statin monotherapy compared to combination therapy. Therefore, additional trials to answer this specific question that are of sufficient duration to capture these outcomes are needed.

We further suggest that future studies focus on high-risk CHD populations and populations with greater burden of cardiovascular disease to determine which strategy provides better short-term improvements in lipid profile and long-term clinical benefits. These populations would include patients with diabetes and preexisting cardiovascular disease, as well as Black and Native American populations.[20] It may be worthwhile to explore differences between men and women, as the ACCORD trial showed benefit of combination therapy with fibrate in men and potential harms with this combination therapy in women.[13] These studies would have tremendous impact on clinical practice, as these patients are the most likely to need a more aggressive lipid-modifying regimen.

While head-to-head comparisons of a combination regimen to intensification of statin therapy may answer important clinical questions, these trials do not help clinicians decide between different combination therapy options. The next step to inform clinical decisionmaking would be to help clinicians how to select the most appropriate lipid-modifying regimen from all available options. We suggest that future studies conduct head-to-head comparisons of multiple combination regimens against each other as well as intensification of statin monotherapy to address this need.

Conclusions

The combination of statin with ezetimibe or bile acid sequestrant lowered LDL-c better than intensification of statin monotherapy, while intensification of statin monotherapy was preferable in reducing LDL-c when considering combination therapy of statin with niacin or fibrate. Combination of statin with ezetimibe, niacin, or fibrate raised HDL-c better than intensification of statin monotherapy. Additional studies need to evaluate long-term clinical benefits and factors that influence medication adherence such as tolerability and harms, which would provide important information for clinical decisionmaking, patient choice, and clinical practice guidelines.

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Introduction

Cardiovascular Disease (CVD)

Cardiovascular disease (CVD) includes conditions such as coronary heart disease, stroke, heart failure, arrhythmia, heart valve disease, congenital heart disease, and hypertension. The American Heart Association (AHA) has estimated that CVD affects 83.6 million individuals, contributes to 32.3 percent of deaths, and is a leading cause of disability.[1] CVD prevalence has been projected to rise in the future, with over 40 percent of the U.S. population having CVD by 2030.[2] In addition, the total direct medical costs attributable to CVD are expected to increase from $273 billion in 2010 to $818 billion by 2030. [3]

While CVD is the leading cause of death for men and women, some gender differences exist. The CVD death rate for U.S. women is estimated as 123.7 per 100,000 women, while for U.S. men the estimated CVD death rate is 249.8 per 100,000 men. [1] In addition, there are differences in rates of CVD by race/ethnicity. Recently, the Centers for Disease Control examined differences in self-reported CVD by race/ethnicity. They found that Native American and black men self-reported higher proportions of CVD (13.4% and 9.4%, respectively) as compared to the median percentage of men with CVD among the locations surveyed (8.8%), while Hispanic and Asian men had lower percentages (7.7% and 6.6%, respectively).[4] A similar trend was seen for women; the median percentage of women with CVD was 6.3 percent, while 12.4 percent of Native American women, 10.3 percent of black women, 5.7 percent of Hispanic women, and 4.4 percent of Asian women reported having CVD.[4]

Atherosclerotic CVD and Lipids

Atherosclerosis plays a major role in the development of atherosclerotic CVD, which is a subset of CVD that includes coronary heart disease (CHD), cerebrovascular disease, and peripheral artery disease. The American Heart Association estimates that atherosclerotic CVD affects 15.4 million Americans. [1] CHD, which includes coronary artery disease (CAD), myocardial infarction (MI), unstable angina (UA), and heart failure, is a leading cause of death for both men and women in the U.S.[5]) By 2030, the prevalence of CHD will rise by 16.6 percent and result in over $106 billion in direct healthcare costs. [3]

Role of LDL in Atherosclerotic CVD

Abnormal lipoprotein metabolism predisposes individuals to atherosclerosis, especially increased concentrations of apo B-100-containing low-density lipoprotein (LDL-c). Oxidized LDL-c is atherogenic, causing endothelial damage, alteration of vascular tone, and recruitment of monocytes and macrophages. [6] Many studies have underscored the importance of LDL-c in development of atherosclerotic CVD. [7,8] Due to the consistent and robust association of higher LDL-c levels with atherosclerotic CVD across experimental and epidemiologic studies, therapeutic strategies to decrease risk have focused on LDL-c reduction as the primary goal. While the prevalence of elevated LDL-c levels among adults has decreased by 33 percent from 1999 to 2006, the most recent estimates still report that 28 percent of U.S. adults have elevated LDL-c.[1]

Role of Other Lipoproteins in Atherosclerotic CVD

In contrast to LDL-c, high-density lipoprotein (HDL-c) has a protective role against atherosclerotic CVD. HDL-c may inhibit LDL-c oxidation through various enzymes, as well as reverse cholesterol transport.[6] These enzymes stop the formation of or destroy the atherogenic, oxidized LDL-c, thereby preventing the inflammatory reaction that results in endothelial damage and plaque formation. Epidemiologic studies have demonstrated an inverse association between HDL-c and CVD. Low HDL-c levels are independent predictors of CHD [9,10] and have been associated with increased CVD risk among patients without vascular disease at baseline.[11] Triglyceride levels may also have effects on atherosclerotic CVD. While LDL-c and HDL-c may have the strongest effects on CVD risk, a meta-analysis examining the association between triglycerides and CVD risk has found that elevated triglycerides confers a 14 percent increase risk for men and a 37 percent increased risk for women after adjusting for HDL-c and other risk factors.[12]

Evidence for Lipid Modifying Therapy

Lipid-modifying medications include 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, bile acid sequestrants, cholesterol absorption inhibitor, fibric acids, nicotinic acid, and omega-3 fatty acids, which have various mechanisms of action and pharmacokinetic properties. Table 1 provides an overview of the expected lipid effects of these agents based on mechanism of action and reported effects in clinical trials.

Table 1: Lipid modifying agents and their expected lipid effects

Agent	LDL	HDL	Triglycerides
HMG-CoA Reductase Inhibitors	Decrease	Increase	Decrease
Bile Acid Sequestrants	Decrease	None	Limited
Cholesterol Absorption Inhibitor	Decrease	None	None
Fibric Acids	Decrease	Increase	Decrease
Nicotinic Acid	Decrease	Increase	Decrease
Omega-3 Fatty Acids	Limited	None	Decrease

Mechanism of Action of HMG-CoA Reductase Inhibitors

The most widely prescribed lipid-lowering agents are the HMG-CoA reductase inhibitors or "statins." These agents inhibit the enzyme, HMG-CoA reductase, which is the catalyst for the rate-limiting step in cholesterol synthesis in the liver.[13] As a result, the lower intracellular cholesterol concentration triggers increased expression of hepatic LDL receptors, which then enhances the clearance of LDL-c from the plasma.[14] Statins may also inhibit hepatic synthesis of apolipoprotein B-100, as well as decrease the synthesis and secretion of other lipoproteins.[15,16] Studies have demonstrated that statins result in significant reductions in LDL-c, and modest increases in HDL-c.[17,18]A recent meta-analysis of trials targeting LDL-c reduction with statins found that reducing LDL-c by 39 mg/dL resulted in reductions in the annual incidence of MI, revascularization, and ischemic stroke by one fifth.[19] Statins may also contribute to regression of atherosclerosis,[20] stabilize plaque,[21] decrease inflammation,[22] and reduce endothelial dysfunction.[23] Statins have shown clear benefits in overall mortality and in primary and secondary prevention of CHD. In patients without CHD, statins have decreased nonfatal myocardial infarctions,[24] incidence of a first major coronary event,[25,26] and all-cause mortality.[27] In patients with known CHD or CHD risk equivalents (e.g., diabetes), statins reduce major coronary events, cardiovascular mortality, and all-cause mortality.[28,29] Another meta-analysis found that statin use reduced all-cause mortality by 17 percent, reduced fatal and non-fatal CVD endpoints by 30 percent, and reduced the revascularization rates by 34 percent.[30] There are 7 statins currently approved by the FDA: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin.

Mechanism of Action of Bile Acid Sequestrants

Bile acid sequestrants (BAS) bind bile acids in the bowel, which prevents them from being reabsorbed the intestine and effectively interrupts their enterohepatic circulation.[31] As a result, the liver increases its synthesis of cholesterol and uptake of circulating LDL-c to produce more of these bile acids. This process ultimately results in the lowering of circulating LDL-c. BAS have no effects on HDL. There are 3 BAS currently approved by the FDA: cholestyramine, colesevelam, and colestipol.

Mechanism of Action of Cholesterol Absorption Inhibitor

Cholesterol absorption inhibitor blocks the Niemann-Pick C1-like protein (NPC1L1) in the small intestine, which thereby prevents the uptake of cholesterol from the gut. Ultimately, this process leads to relative depletion of cholesterol in the liver, which responds by increasing cholesterol synthesis and uptake of circulating LDL-c.[32,33] This process ultimately results in the lowering of circulating LDL-c. Cholesterol absorption inhibitor has no effects on HDL-c.[34,35] Currently, there is one FDA approved cholesterol absorption inhibitor, ezetimibe.

Mechanism of Action of Fibric Acids

Fibric acids or "fibrates" may modulate lipoprotein levels through a variety of mechanisms including induction of lipoprotein lipolysis, induction of fatty acid uptake, reduction of hepatic triglyceride production, increased removal of LDL-c particles, and increased production of HDL-c.[36] Typically, fibrates will result in a mild decrease in LDL-c, mild increase in HDL-c, and significantly reduce triglycerides. There are 3 fibrates currently approved by the FDA: fenofibrate, fenofibric acid, and gemfibrozil.

Mechanism of Action of Nicotinic Acid

Nicotinic acid or "niacin" inhibits the synthesis of LDL-c, as well as delays clearance of circulating HDL-c.[37] Typically, niacin moderately decreases LDL-c and moderately increases HDL-c.[38,39] Niacin has demonstrated modest benefit in decreasing nonfatal recurrent MI, but has not lead to decreases in mortality.[40] Niacin is the only nicotinic acid currently approved by the FDA.

Mechanism of Action of Omega-3 Fatty Acids

Dietary consumption of marine-sourced omega-3 fatty acids has been linked with positive cardiovascular benefits for many years. Available prescription omega-3 fatty acids contain eicosapentaenoic acid (EPA) with/without docosahexaenoic acid (DHA). While the mechanism of omega-3 fatty acids is not fully understood, they have been hypothesized to inhibit acyl CoA:1,2 diacylglycerol acyltransferase, increase hepatic beta-oxidation, reduce the hepatic synthesis of triglycerides, or increase plasma lipoprotein lipase activity. Typically, omega-3 fatty acids lead to decreases in triglycerides and potentially increase large particle LDL-c, which may be less atherogenic.[41] These medications have been linked with reduced risk of death, nonfatal

MI and nonfatal stroke.[42] There are currently 2 omega-3 fatty acids approved by the FDA: omega-3 acid ethyl ester and icosapent ethyl.

Current Guidelines for Lipid Modifying Therapy

The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III provides guidelines on when to initiate lipid-lowering therapy as well as recommended LDL-c targets for optimal CHD risk reduction.[2] The NCEP ATP III report established three CHD risk strata along with guidelines regarding the initiation of treatment and therapeutic targets based on these LDL-c cutoffs. ATP III defined the highest risk individuals as those with established CHD, other clinical atherosclerotic CVD, or multiple risk factors for atherosclerotic CVD. These high-risk individuals have a 10-year CHD risk greater than 20 percent, and their LDL-c target is less than 100 mg/dL. Moderate risk patients are those with 2 or more risk factors and a 10-year CHD risk less than 20 percent. The LDL target for moderate risk patients is less than 130 mg/dL, but the threshold for starting drug therapy depends on their CHD risk level. For moderate risk patients with a 10-year CHD risk of 10-20 percent, providers should consider drug therapy if the LDL-c is above 130 mg/dL. While for moderate risk patients with a 10-year CHD risk less than 10 percent, drug therapy does not need to be considered until the LDL-c reaches 160 mg/dL.

Following release of ATP III in 2002, five major trials were published which led to a revision of these guidelines in 2004.[43] These revised guidelines expanded the population for whom lipid lowering therapy was recommended. Diabetes was now considered as a CHD risk equivalent, which placed these patients in the high-risk category. In addition, more aggressive targets were advocated as a therapeutic option for the highest risk individuals. These “very high-risk patients” were defined as those with acute coronary syndromes, multiple major risk factors (especially diabetes and smoking), severe and poorly controlled risk factors, and multiple risk factors for metabolic syndrome. The previous target of LDL-c below 100 mg/dL was supplemented with an optional goal of LDL-c below 70 mg/dL in these very high-risk patients who already have baseline LDL-c below 100 mg/dL. While this new, lower target of LDL-c was supported by reductions in vascular events in two trials that examined these high risk subgroups,[44,45] additional trials are needed to confirm this finding.

The National Heart, Lung, and Blood Institute commissioned an update of these guidelines (ATP IV), which many anticipate will be released later in 2013. Based upon the revised recommendations from organizations such as the American Diabetes Association (ADA) and the American College of Cardiology Foundation (ACCF), ATP IV may expand focus of lipid lowering beyond LDL-c with greater emphasis on non-HDL-c and ApoB.[46] These guidelines may also recommend new treatment goals for LDL-c, where the goal for the highest risk patients would be LDL-c <70 mg/dL, similar to ADA and ACC recommendations.[46] The ACCF, AHA, American College of Physicians, and others have advocated for the approach of prescribing at least a moderate dose statin to all patients with ischemic coronary heart disease, regardless of LDL-c value.[47] Some experts have advocated that ATP IV should not recommend LDL-c targets, as little scientific evidence exists to support treating to LDL-c targets, the safety of treating to LDL-c targets is unknown, and some consider tailored treatment to be simpler, safer, and more effective.[48]

Current Controversies in Lipid Modifying Therapy

While statins have demonstrated efficacy in reducing LDL-c and improving cardiovascular disease outcomes, there is ongoing debate as to how to manage patients who do not achieve their LDL-c goals with statin alone. In this scenario, the clinician could consider increasing the dose of the statin or adding a non-statin medication to the regimen. There are potential benefits to treating with multiple agents, as the different mechanisms of action of the other lipid-modifying agents may produce other benefits unlikely to be achieved with statin alone. For example, a fibrate or niacin in combination with a statin may increase HDL-c and decrease triglycerides above what is achieved with statin treatment alone.[49] Combination therapy could result in fewer statin-related side effects (e.g., myalgias and elevated liver transaminases), as lower doses of statin could be used. Conversely, a combination of agents could result in an increase in side effects, as patients may experience the side effects common to both drugs.

Despite the generally favorable effects of combination regimens on surrogate lipid markers in clinical trials, combination regimens have not consistently been shown to improve clinical outcomes.[49,49-51] For example, the ENHANCE trial, which compared ezetimibe + simvastatin to simvastatin along on carotid intima-media thickness (CIMT) in patients with hyperlipidemia, showed no regression in CIMT despite significantly lower LDL-c levels in the combination therapy group.[52] Because CIMT is still a surrogate for clinical outcomes, the IMPROVE-IT trial aims to compare ezetimibe + simvastatin to simvastatin on cardiovascular death, MI, revascularization, or stroke.[53] This trial is still ongoing. In the ACCORD trial, combination of fenofibrate and simvastatin did not reduce the rates of cardiovascular deaths, MI or stroke more than simvastatin monotherapy among patients with diabetes.[54] This combination therapy conferred benefit for men, and possible harms for women. In the AIM-HIGH trial, patients with preexisting atherosclerotic CVD received niacin + simvastatin or simvastatin monotherapy.[49]While the patients taking combination therapy had greater increases in their HDL-c, there were no benefits on incidence of cardiovascular death, MI, stroke, or revascularization procedures. Some concern exists that combination regimens may worsen clinical outcomes, such as the potential worsening of atherosclerosis reported with the combination of statin and ezetimibe.[51] Similarly, the evidence for the benefits of intensification of statin monotherapy is unclear, as there is not a consistent mortality benefit of this therapy among patients with stable CHD.[28,44,55-58]

2013 Update of the Comparative Effectiveness Review: Overview

In 2009, the Agency for Healthcare Research and Quality (AHRQ) released an evidence report examining lipid-modifying agents.[59,60] This prior review initially intended to examine the long-term benefits and rates of serious adverse effects of co-administration of different lipid-lowering agents vs. higher dose statin monotherapy for patients at high CHD risk (ten-year risk > 20%). However, the authors found a paucity of evidence to address this question, so conducted additional analyses unrestricted by patient risk, statin type or statin dose. Despite this increase in scope, the authors concluded that there was insufficient evidence to determine whether combination therapy held benefit over monotherapy. Since the initial review, additional small and large trials on efficacy and safety outcomes have been published. The evidence base for all three key questions has been expanded, which necessitates an update of the prior review.

To provide additional guidance to clinicians treating patients with moderate or high CHD risk, this update review addresses long-term benefits and rates of serious adverse events (SAEs) associated with co-administration of different lipid-modifying agents compared with higher potency statin monotherapy. We included studies examining patients at moderate and high CHD risk, defined as a 10-year CHD risk greater than 10 percent or LDL-c greater than 160 mg/dL, as these patients may require intensive lipid modifying therapy to achieve their LDL-c goals. Studies focusing on lower risk patients with a 10-year CHD risk less than 10 percent were excluded, as these patients are likely to achieve their LDL-c goal with typical statin monotherapy. This update review additionally examines surrogate markers of CHD events including lipid levels and atherosclerosis, as well as side effects/tolerability and medication adherence. Similar to the prior review, we sought to evaluate clinical/surrogate benefits and harms among the following subgroups: females, patients older than 80, diabetics, patients with established vascular disease, and participants of African and Asian descent as well as Hispanics.

Scope and Key Questions

We aimed to compare the effectiveness, safety, and tolerability of combination of statin and other lipid-modifying medication to intensification of statin monotherapy. Our scope was limited to comparing combination of statin with other lipid-modifying medication to intensification of statin monotherapy as proposed in the key questions. While several trials have shown that non-statin monotherapy may not improve clinical outcomes, we did not include non-statin monotherapy as a comparison group because it was outside the scope of this update. We sought to answer the questions below by reviewing trials of adults that compared a higher potency of statin monotherapy to a lower potency statin in combination with another agent (bile acid sequestrant, ezetimibe, fibrate, niacin, or omega-3 fatty acid).

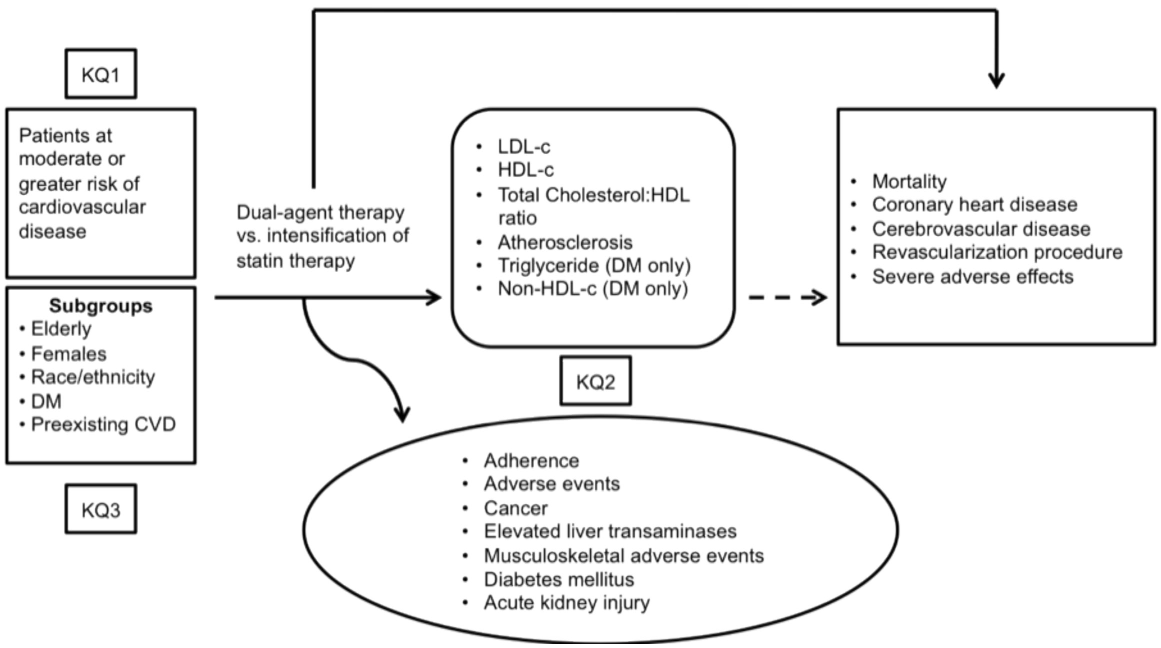
The specific Key Questions (KQ) are:

KQ 1: For patients who require intensive lipid-modifying therapy, what are the comparative long-term benefits and rates of serious adverse events of co-administration of different lipid-modifying agents (i.e., a statin plus another lipid-modifying agent) compared with higher dose statin monotherapy?

KQ 2: Do these regimens differ in reaching LDL targets (or other surrogate markers), short-term side effects, tolerability, and/or adherence?

KQ 3: Compared with higher dose statins and to one another, do combination regimens differ in benefits and harms within subgroups of patients?

Figure 1: Analytic framework for comparative effectiveness of lipid-modifying agents



KQ= key question, CVD= cardiovascular disease, DM= diabetes mellitus, HDL= high density lipoprotein; LDL= low density lipoprotein

Methods

Topic Development

This review is an update of an evidence report completed in 2009.[60] The summary of changes from the previous systematic review is shown in Table 2. The protocol for our review was posted on the AHRQ Web site (www.effectivehealthcare.ahrq.gov).

Table 2: Summary of changes from prior report

Population	We included adults at moderate and high risk of cardiovascular disease (the prior report had no restrictions by patient CVD risk level). We specifically excluded studies of patients with homozygous familial hypercholesterolemia.
Intervention	We included drugs that were not FDA-approved at the time of the prior review.
Outcomes	We added diabetes mellitus and acute kidney injury/chronic kidney disease as potential harms.
Type of Study and Timing	We reviewed nonrandomized studies that were extensions of RCTs. The prior evidence report considered any nonrandomized study over 24 weeks duration.
Data Synthesis	In order to avoid multiple comparisons across numerous permutations of lower versus higher dose statins, we grouped statins based on their potency to reduce LDL-c.

Search Strategy

Using the same basic search rules used for the original report (with the addition of terms for newly added drugs), we searched the following databases for primary studies: MEDLINE, Embase®, and the Cochrane Central Register of Controlled Trials (CENTRAL). Our search strategy for MEDLINE is shown in Appendix B. The search for the prior review included MEDLINE from 1966 to May 2009, Embase from 1980 to May 2009, and The Cochrane Library to the third quarter of 2008. We included an overlap in search dates, per AHRQ guidance on updating reviews,[61] searching MEDLINE from May 2008 to January 2013, Embase from May 2008 to January 2013, and The Cochrane Library from the fourth quarter of 2007 to January 2013. We also reviewed references from relevant review articles. Pharmaceutical companies who produce the drugs included in this review were asked to provide information as Scientific Information Packets (SIPs) about pertinent studies (published or unpublished). The search will be updated during the peer review process.

Study Selection

Abstracts were screened independently by two trained reviewers, and were excluded if both reviewers agreed that the article met one or more of the exclusion criteria (see inclusion and exclusion criteria listed in Table 3 and the Abstract Screen Form in Appendix C). In brief, we included randomized controlled trials (RCT) of adults that compared a higher potency of statin monotherapy to a lower potency statin in combination with another agent (bile acid sequestrant, ezetimibe, fibrate, niacin, or omega-3 fatty acid). The clinical outcomes of interest were mortality, coronary heart disease events, cerebrovascular events, revascularization procedures, and serious adverse events, while our surrogate clinical outcomes included lipid measures (e.g., LDL-c, HDL-c), atherosclerosis, and medication adherence. Triglycerides and non-HDL-c were only considered for diabetic subgroup. Adverse effects included cancer, elevated liver transaminases, musculoskeletal adverse events, diabetes mellitus, and acute kidney injury. Given the limited duration of many RCTs, we also considered observational trials to examine clinical outcomes, serious adverse events and harms. As in the prior evidence report, we considered non-randomized comparative studies of 24 weeks or more in duration for clinical outcomes, serious adverse events, and harms, which were extensions of controlled clinical trials. These are trials in which patients are unblinded and continue to receive the therapies they were originally assigned. Finally, we also searched FDA reports for serious adverse events and harms. Differences between reviewers regarding abstract eligibility were resolved through consensus.

Citations promoted on the basis of abstract screen underwent independent paired-reviewer screen using the full text article (Appendix C, Article Screen Form). Differences regarding article inclusion were resolved through consensus. At this level, we also screened all studies included in the prior review to ensure that they met the current eligibility criteria.

Table 3: List of inclusion/exclusion criteria

Population and condition of interest	Adults with moderate (10-year CHD risk 10-20% or LDL≥160 mg/dL) or high (10-year CHD risk≥20% or LDL≥190 mg/dL) cardiovascular disease risk *Excluded* studies if they included only adults with low cardiovascular disease risk (CHD risk<10% or LDL<160 mg/dL) *Excluded* studies that included only patients with homozygous familial hypercholesterolemia (FH)
Interventions and approaches	Studies must have evaluated a combination regimen of interest Included studies of bile acid sequestrants + statin Included studies of ezetimibe + statin Included studies of fibrates + statin Included studies of niacin + statin Included studies of omega-3 fatty acids + statin *Excluded* studies of lifestyle modifications *Excluded* studies of drugs approved only for the treatment of homozygous FH *Excluded* studies of drugs not approved by the FDA or investigational drug *Excluded* studies of prepackaged medications that contained non lipid-lowering medications
Comparisons of interest	Included comparisons of higher potency statin monotherapy *Excluded* studies if a study statin monotherapy was of the same or lower potency than combination arm *Excluded* studies if there was no comparison, only placebo comparison, or comparison to other combination therapy regimen.
Outcomes and Timing	Clinical outcomes including mortality, cardiovascular events, cerebrovascular events, revascularization procedures at any time point Surrogate outcomes including LDL-c, HDL-c, TC:HDL-c ratio, NCEP ATP IIL LDL-c target attainment, measures of atherosclerosis (e.g., carotid intimal media wall thickness, coronary artery calcification score, etc) at any time point. Triglycerides and non-HDL-c in diabetes subgroup. Adherence and harms outcomes including adherence, serious adverse events, withdrawal due to adverse events, cancer, elevated liver transaminases, adverse musculoskeletal events, diabetes mellitus, acute kidney injury at any time point
Type of study	Included studies with any sample size that met all other criteria. Included studies from the prior report that met all other criteria. Included randomized controlled trials () Included non-randomized extension of clinical trial over 24 weeks duration (clinical outcomes, SAE and harms only), and Included FDA reports (SAE and harms only) *Excluded* studies with other observational designs. *Excluded* studies with no original data (reviews, editorials, comments, letters, modeling only studies). *Excluded* studies published only as abstracts. *Excluded* qualitative studies. *Excluded* crossover trials with fewer than 4 weeks washout and/or lacking paired observation, within person differences, or pre-crossover data. *Excluded* non-English publications.

CHD= coronary heart disease; FH =familial hypercholesterolemia; FDA= Food and Drug Administration; HDL= high density lipoprotein; LDL= low density lipoprotein; RCT= randomized controlled trial; SAE= serious adverse event; TC= total cholesterol

Data Abstraction and Data Management

We used DistillerSR (EvidencePartners, 2010) to manage the screening process. We uploaded to the system all citations identified by the search strategies.

We created and pilot tested standardized forms for data extraction (Appendix C). We used the Systematic Review Data Repository™ (SRDR) for data abstraction. Data were exported from SRDR into a project-specific database (Access, Microsoft, Redmond, WA) to serve as archived copy and to create evidence tables and summary tables.

Reviewers extracted information on general study characteristics (e.g., study design, study period, and followup), study participants (e.g., age, sex, race/ethnicity, etc.), eligibility criteria, interventions (e.g., medication name, medication dose), outcome measures and the method of ascertainment, and the results of each outcome including measures of variability. One reviewer completed data abstraction and a second reviewer confirmed the first reviewer's abstraction for completeness and accuracy. Because data previously abstracted from the trials included in the prior review were incomplete for our needs, we abstracted the data from the studies that met the current eligibility criteria in order to have a complete repository of data for analysis. Reviewer pairs included personnel with both clinical and methodological expertise. We resolved differences between reviewer pairs through discussion and, as needed, through consensus among the larger group of investigators.

Risk of Bias Assessment

We used the Cochrane Collaboration's tool for assessing the risk of bias of controlled studies.[62] Two trained reviewers independently assessed the included studies according to the guidelines in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions. For studies included from the prior review, we used the prior quality assessments reported, which were based on the Jadad Score.

Data Synthesis

For each KQ, we created a detailed set of evidence tables containing all information abstracted from eligible studies. We integrated the results of all studies (RCTs + NRSs) qualitatively. In all comparisons, we noted that the evidence base uses different statins both within studies (monotherapy arms uses one statin and combination therapy uses a different statin) and across studies. In addition, a variety of statin doses were also used across studies. Therefore, synthesizing data by statin and statin dose would limit the number of studies amenable to pooling. A recent systematic review grouped statins and statin doses based on their potency to reduce LDL-c (Table 4).[63] We opted to use this potency strategy to group together different statins and statin doses to make comparisons, which increased out number of studies amenable to pooling. This represents a change from the approach used in the original review, in which statins were grouped according to dose.

Table 4: List of different dosing of specific statins based on potency to reduce LDL-c

Statin	Atorvastatin (mg/day)	Fluvastatin (mg/day)	Fluvasatin XL (mg/day)	Lovastatin (mg/day)	Pitavastatin (mg/day)	Pravastatin (mg/day)	Rosuvastatin (mg/day)	Simvastatin (mg/day)
Low Potency (<30% LDL reduction)	5	20 and/or 40	--	5 and/or 10 and/or 20	1	10 and/or 20 and/or 40	--	10
Mid Potency (30-40% LDL reduction)	10	80	80	40 and/or 80	2 and/or 4	80	5 and/or 10	20
High Potency (>40% LDL reduction)	20 and/or 40 and/or 80	--	--	--	--	--	20 and/or 40	40 and/or 80*

*Studies that use simvastatin 80mg in statin naïve patients will be excluded.

Meta-analysis was considered for outcomes selected as most important for grading the strength of evidence (see below). Studies were grouped such that meta-analyses included the same potency comparisons (i.e., high potency monotherapy versus mid potency combination therapy). For studies that had two monotherapy arms of the same potency, we used only one of these arms as the comparator to the combination arm(s). We used the following rules to select which monotherapy arm to use:

1. If the arms use the same statin, we used the arm with the higher dose.
2. If the arms use different statins, we selected the arm based on the following prioritization of statin agent if it met higher potency criteria: rosuvastatin, atorvastatin, simvastatin, lovastatin, pravastatin, fluvastatin.[64] We identified no studies that used pitavastatin.

We only conducted meta-analyses when there were sufficient data (at least 3 studies of the same design that reported or provided data to calculate SE for difference in differences) and studies were judged to be sufficiently homogenous with respect to key variables (population characteristics, intervention, and outcome). Many studies did not provide sufficient data to calculate SE for difference in differences. When SE was available for most studies included within a specific comparison, we imputed the SE for these other studies. We averaged the reported SE and used this value for the imputed SE.[65] We then conducted sensitivity analysis by completing meta-analyses with and without the imputed SE.

For studies amenable to meta-analysis, we calculated a weighted mean difference using a random effects model with the DerSimonian and Laird formula for continuous outcomes.[66] We evaluated statistical heterogeneity among studies using an I^2 statistic. We had no dichotomous or event outcomes that met our criteria to consider conducting meta-analyses. Given the lack of outcomes meeting our criteria for meta-analysis and significant heterogeneity detected when meta-analyses were conducted (I^2>50%), we report qualitative synthesis of data for most outcomes. We examined the forest plots to identify trials that appeared to have quite different results and considered if these trials had different characteristics. We planned to conduct sensitivity analysis by excluding such trials and rerunning meta-analyses but in all cases we identified no trials meeting this criteria or removing these trials would have left fewer than 3 trials to be pooled. The limited number of studies included in each meta-analysis precluded any further sensitivity analyses of subgroups or meta-regression to determine the source of heterogeneity. All analyses were conducted using STATA versions 11.0 and 12.0 (StataCorp LP).

Strength of the Body of Evidence

We graded the strength of evidence using the grading scheme recommended by the Methods Guide for Effectiveness and Comparative Effectiveness Reviews (Methods Guide).[67] For this report, we graded the strength of evidence for the outcomes determined to be most important: mortality, acute coronary events, revascularization procedures, serious adverse events, and LDL-c.

In assigning evidence grades, we considered the four required domains including risk of bias, directness, consistency and precision. For outcomes where meta-analysis was not conducted, precision was determined based on the measures of dispersion provided by the studies. The body of evidence for a particular outcome was also considered imprecise if the results were inconsistent or sample size across trials was considered insufficient. If judgement could not be made on those factors, optimal information size (OIS) was calculated to determine sufficiency of sample size.

We classified the strength of evidence into four basic categories: 1) "high" grade (indicating high confidence that the evidence reflects the true effect, and further research is very unlikely to change our confidence in the estimate of the effect); 2) "moderate" grade (indicating moderate confidence that the evidence reflects the true effect, and further research may change our confidence in the estimate of the effect and may change the estimate); 3) "low" grade (indicating low confidence that the evidence reflects the true effect, and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate); and 4) "insufficient" grade (evidence is unavailable or does not permit a conclusion). A comparison-outcome pair with high strength of evidence was one with low risk of bias, directness, consistency, and precision. Moderate strength of evidence indicated a high risk of bias was noted or that *two* of the following were observed: a moderate risk of bias, inconsistency, indirectness or imprecision. Low strength of evidence indicated *two* or more of the following: a moderate risk of bias, a high risk of bias, inconsistency, indirectness and imprecision. Our judgments were first based on the ability to make a conclusion (if not able to make a conclusion, then "insufficient" was assigned) and then on the confidence in the conclusion (classified as low, moderate or high with increasing certainty). We considered any study that calculated LDL-c as indirect, as the option to measure LDL-c directly does exist and new evidence exists that the Friedewald equation tends to underestimate LDL-c among high risk patients.[68]

Investigators writing each section completed the strength of evidence grading. The team members reviewed and discussed grading throughout the report writing.

Applicability

Applicability was assessed separately for the different outcomes for the entire body of evidence guided by the PICOS framework as recommended in the Methods Guide.[69] We considered important population characteristics (e.g., women, minorities, diabetics), treatment characteristics (e.g., statin type, statin potency, length of intervention/therapy, dose escalation), and timing that may cause heterogeneity of treatment effects and limit applicability of the findings.

Peer Review and Public Comment

We invited experts to provide external peer review of this review; AHRQ representatives and an associate editor also provided comments. AHRQ will post the draft report on its website for 4 weeks to elicit public comment. We will address all reviewer comments, revising the text as appropriate, and documenting everything in a disposition of comments report that we will be made available 3 months after AHRQ posts the final review on its website.

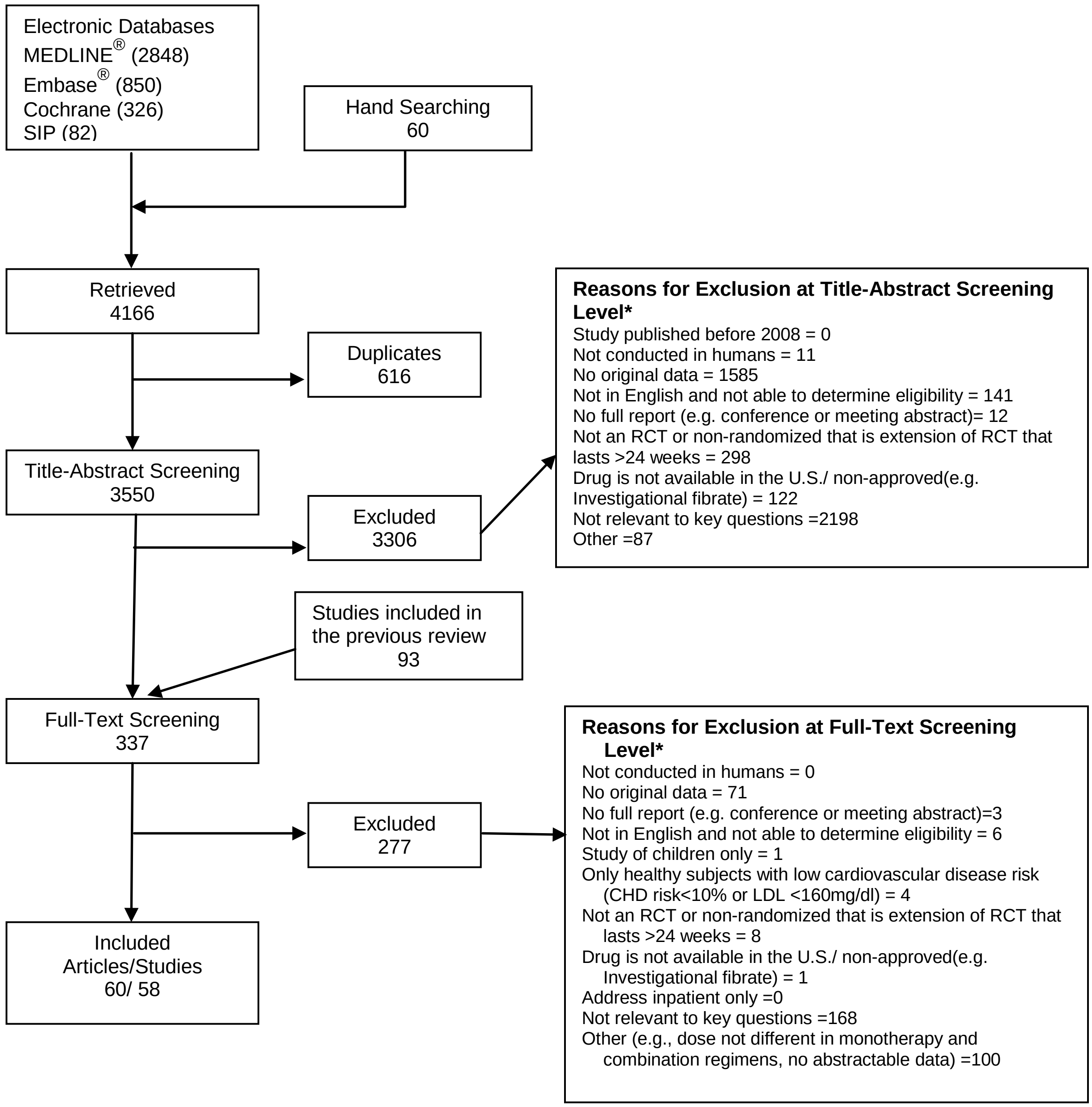
Results

Results of Literature Searches

Figure 2 summarizes the search results. The literature search identified 4,084 unique citations. During the title and abstract screening we excluded 3,306 citations; during the full-text article screening we excluded 277 citations (Appendix D). Of the 14 companies contacted for SIPs, 5 companies responded. One company indicated that no relevant studies had been conducted. Four companies provided SIPs and the references provided by these four companies were carefully crosschecked against our existing database, yielding four new references, none of which were applicable to this review (Appendix E).

Fifty-eight studies, all randomized controlled trials, reported in 60 articles, were included.

Figure 2: Summary of search (number of articles)



* Total exceeds the number of citations in the exclusion box, because citations could be excluded for more than one reason

Overview of included trials by potency and agent

Of the included trials, 6 trials addressed combination therapy with bile acid sequestrant, 38 trials addressed combination therapy with ezetimibe, 8 trials addressed combination therapy with fibrates, 7 trials addressed combination therapy with niacin and statin, and 2 trials addressed comparing combination therapy with omega-3 fatty acid (note that one study addressed multiple two combinations: omega 3 and fibrates). Thirty trials were included from the previous review that met the current eligibility criteria and 28 trials were identified in the new searching (Tables 5 and 6).

Table 5: Randomized trials included in evidence synthesis according to statin potency

Statin	Evidence Report Year	Bile Acid Sequestrants	Ezetimibe	Fibrates	Niacin	Omega-3 Fatty Acids
Low potency combination therapy vs high potency monotherapy	2009	NR	Ballantyne, 2005[70] Bays, 2004[71] Davidson, 2002[72] Goldberg, 2004[73]	Athyros, 2001[74]	NR	NR
	2013	NR	Ahmed, 2008[75] Araujo, 2010[76] Floretin, 2011[77] Lee, 2011[78] Lee, 2012[79] Liberopoulos, 2013[80] Moutzouri, 2011[81] Moutzouri, 2012[82] Okada, 2011[83] Rudofsky, 2012[84]	NR	Airan-Javia, 2009 [85]	NR
Mid potency combination therapy vs high potency monotherapy	2009	Hunninghake, 2001[86] Johansson, 1995[87]	Ballantyne, 2003[88] Ballantyne, 2005[70] Barrios, 2005[89] Bays, 2004[71] Catapano, 2006[90] Constance, 2007[91] Davidson, 2002[72] Gaudiani, 2005[92] Goldberg, 2004[73] Goldberg, 2006[93] McKenney, 2007[94] Piorkowski, 2007[95] Roeters van Lennep, 2008[96] Stein, 2004[97]	Athyros, 2001[74] Shah, 2007[98]	Bays, 2003[99] Capuzzi, 2003[100] McKenney, 2007[94]	NR
	2013	NR	Bardini, 2010[101] Bays, 2011[102] Ben-Yehuda, 2011[103] Cho, 2011[104] Foody, 2010[105] Moutzouri, 2011[81] Okada, 2011[83] Ostad, 2009[106] Pesaro, 2012[107] Robinson, 2009[108] Tomassini, 2009[109]	Agouridis, 2011a [111] Agouridis, 2011b [112] Jones, 2009[113] Makariou, 2012 [114] Mohiuddin, 2009[115] Roth, 2010[116] Shah, 2007[117]	NR	Agouridis, 2011a [111] Agouridis, 2011b [112] Makariou, 2012 [114]

Statin	Evidence Report Year	Bile Acid Sequestrants	Ezetimibe	Fibrates	Niacin	Omega-3 Fatty Acids
			Zieve, 2010[110]			
Low potency combination therapy vs mid potency monotherapy	2009	Barbi, 1992[118] Ismail, 1990[119] PMSG II, 1993[120] Knapp, 2001[121] Schrott, 1995[122]	Ballantyne, 2005[70] Bays, 2004[71] Davidson, 2002[72] Feldman, 2004[123] Goldberg, 2004[73] Kerzner, 2003[124]	NR	Hunninghake, 2003[125] Insull, 2004[126]	NR
	2013	NR	Averna, 2010[127] Hamdan, 2011[128] Kawagoe, 2011[129] Okada, 2011[83] Yamazaki, 2013[130]	Farnier, 2011[131]	NR	NR

NR= not reported; PMSG II= Pravastatin Multicenter Study Group II.

Table 6: Randomized controlled trials included in evidence synthesis according to statin agent

Statin	Evidence Report Year	Bile Acid Sequestrants	Ezetimibe	Fibrates	Niacin	Omega-3 Fatty Acids
Atorvastatin	2009	Hunninghake, 2001[86]	Ballantyne, 2003[88] Piorkowski, 2007[95] Stein, 2004[97]	NR	NR	NR
	2013	NR	Ben-Yehuda, 2011[103] Hamdan, 2011[128] Lee, 2011[78] Lee, 2012[79] Ostad, 2009[106] Zieve, 2010[110]	NR	NR	NR
Fluvastatin	2009	NR	NR	NR	NR	NR
	2013	NR	Kawagoe, 2011[129]	NR	NR	NR
Lovastatin	2009	Schrott, 1995[122]	Kerzner, 2003[124]	NR	Hunninghake, 2003[125] Insull, 2004[126]	NR
	2013	NR	NR	NR	NR	NR
Pitavastatin	2009	NR	NR	NR	NR	NR
	2013	NR	NR	NR	NR	NR
Pravastatin	2009	Barbi, 1992[118] Ismail, 1990[119] PMSG II, 1993[120]	NR	NR	NR	NR
	2013	NR	NR	NR	NR	NR
Rosuvastatin	2009	NR	NR	NR	Capuzzi, 2003[100]	NR
	2013	NR	Bays, 2011[102] Yamazaki, 2013[130]	Agouridis, 2011a [111] Agouridis, 2011b [112] Jones, 2009[113] Makariou, 2012 [114]	NR	Agouridis, 2011a [111] Agouridis, 2011b [112] Makariou, 2012 [114]
Simvastatin	2009	Johansson, 1995[87] Knapp, 2001[121]	Bays, 2004[71] Davidson, 2002[72] Feldman, 2004[123] Gaudiani, 2005[92] Goldberg, 2004[73]	NR	NR	NR
	2013	NR	Araujo, 2010[76] Averna, 2010[127] Bardini, 2010[101] Floretin, 2011[77] Liberopoulos, 2013[80] Moutzouri, 2012[82] Pesaro, 2012[107]	Mohiuddin, 2009[115]	Airan-Javia, 2009 [85]	NR

Statin	Evidence Report Year	Bile Acid Sequestrants	Ezetimibe	Fibrates	Niacin	Omega-3 Fatty Acids
			Rudofsky, 2012[84]			
Mixed Statins	2009	NR	Ballantyne, 2005[70] Barrios, 2005[89] Catapano, 2006[90] Constance, 2007[91] Goldberg, 2006[93] McKenney, 2007[94] Roeters van Lennep, 2008[96]	Athyros, 2001[74] Shah, 2007[98]	Bays, 2003[99] McKenney, 2007[94]	NR
	2013	NR	Ahmed, 2008[75] Cho, 2011[104] Foody, 2010[105] Moutzouri, 2011[81] Okada, 2011[83] Robinson, 2009[108] Tomassini, 2009[109]	Farnier, 2011[131] Roth, 2010[116] Shah, 2007[117]	NR	NR

NR= not reported; PMSG= II Pravastatin Multicenter Study Group II.

Results by Combination Therapy Regimen

Combined Lipid-Modifying Therapy with Statin and Bile Acid Sequestrant versus Intensification of Statin Monotherapy

Study Characteristics

We included 6 trials (410 participants in eligible arms) that compared bile acid sequestrant plus statin to intensification of statin monotherapy. The 6 trial results were reported in 7 articles.[86,87,118-122] All trials were parallel arm randomized controlled trials. One trial took place in Europe,[87] and all others took place in North America. All trials were multicenter, except for one single center trial.[118,119] Eligibility criteria were similar across all trials. All trials included a dietary run in, followed by treatment ranging from 4 weeks to 24 weeks in duration. Two trials compared high potency statin monotherapy to mid potency statin in combination therapy.[86,87] The other four trials compared mid potency statin monotherapy to low potency statin in combination therapy.[118-122]

Population Characteristics

The average participant was in their 50s with the mean age across trials ranging from 51-61 years. The number of female participants varied between trials. Race was reported in only two trials, where the majority of participants were white.[120,121] Smoking status, prior cardiovascular disease, revascularization events, and diabetes were not consistently reported across trials. When reported, no significant between group differences existed in the trials.[87,120-122]

Interventions

Two trials compared high potency statin monotherapy to mid potency statin in combination with colsevelam[86] or colestipol.[87] These monotherapy arms used atorvastatin and simvastatin, and the combination arms used atorvastatin and simvastatin. Four trials compared mid potency statin monotherapy to low potency statin in combination with cholestyramine[118-120], colsevelam[121], or colestipol.[122] These trials used lovastatin, pravastatin and simvastatin in the monotherapy arms, and lovastatin, pravastatin and simvastatin in the combination therapy arms.

Outcomes

Key Points

- **Long-Term Benefits**
  - There is insufficient evidence to compare the long-term benefits of combined lipid-modifying therapy with a bile acid sequestrant and statin to intensification of statin monotherapy within any potency comparison.
- **Serious Adverse Events**
  - There is insufficient evidence to compare the serious adverse events of combined lipid-modifying therapy with a bile acid sequestrant and statin to intensification of statin monotherapy.
- **Surrogate Outcomes**

- A low potency statin combined with bile acid sequestrant is more effective than mid potency statin monotherapy for lowering LDL-c (SOE: moderate). There is insufficient evidence within other potency comparisons.
    - There is insufficient evidence to evaluate the effectiveness combined lipid-modifying therapy with a bile acid sequestrant and statin on raising HDL-c as compared to intensification of statin monotherapy within any potency comparison.
- **Short-Term Side Effects**
    - There is insufficient evidence to compare the rates of elevated liver transaminases between combined lipid-modifying therapy with a bile acid sequestrant and statin to intensification of statin monotherapy within any potency comparison.
    - There is insufficient evidence to compare the rates of elevated creatinine phosphokinase between combined lipid-modifying therapy with a bile acid sequestrant and statin to intensification of statin monotherapy within any potency comparison.
- **Adherence**
    - There is insufficient evidence to compare medication adherence between combined lipid-modifying therapy with a bile acid sequestrant and statin to intensification of statin monotherapy within any potency comparison.
- **Subgroups**
    - There is insufficient evidence to compare the long-term benefits and harms of combined lipid-modifying therapy with a bile acid sequestrant and statin to intensification of statin monotherapy within any potency comparison among any subgroup.

Long-term benefits and serious adverse events (KQ1)

No study reported on the comparative effectiveness of bile acid sequestrant plus statin on long-term benefits or rates of serious adverse events as compared to intensification of statin monotherapy among adults. We graded the strength of evidence for mortality, acute coronary events, revascularization procedures, and serious adverse events as insufficient.

Surrogate outcomes, short-term side effects and adherence (KQ2)

All included RCTs evaluated surrogate outcomes including LDL-c and HDL-c. In several RCTs, medication adherence and short-term side effects were evaluated including elevated liver transaminases and withdrawal due to adverse events. We identified no studies that compared high potency statin monotherapy to low potency statin combination therapy. We identified no eligible non-randomized extensions of RCTs or FDA reports.

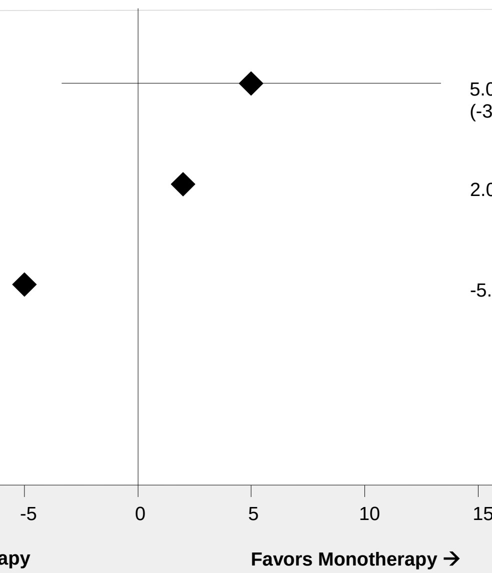
LDL-c

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**

Two trials reported on mean percent LDL-c change.[86,87] At 4 weeks, one trial found that statin monotherapy lowered LDL-c 7 percent more than combination therapy.[86] At 12 weeks, the other trial showed that combination therapy with colestipol 10g + simvastatin 20mg lowered LDL-c 5 percent more than statin monotherapy. However, the other combination arm in this trial, which used a lower dose of colestipol (5g) in combination with simvastatin 20mg, was less effective than statin monotherapy at reducing LDL-c (between group difference 2 percent that favored monotherapy). Overall, the results showed inconsistent effects on lowering LDL-c,(Figure 3) we graded the strength of evidence as insufficient (Table 7).

Figure 3: Mean difference in percent LDL change from baseline to time point comparing mid potency combination therapy to high potency monotherapy with bile acid sequestrants

Author, Year	Statin Monotherapy	Combination Therapy	Monotherapy Baseline LDL-c (mg/dL)	Combination Baseline LDL-c (mg/dL)	Between Groups Difference (95% CI)	Timepoint weeks	N
Hunninghake, 2001	ATV 80mg	Colsevelam 3.8g + ATV 10mg	182	187	5.0 (-3.4, 13.4)	4	38
Johansson, 1995	SMV 40mg	Colestipol 5g + SMV 20mg	222	218	2.0	12	55
Johansson, 1995	SMV 40mg	Colestipol 10g + SMV 20mg	222	224	-5.0	12	54



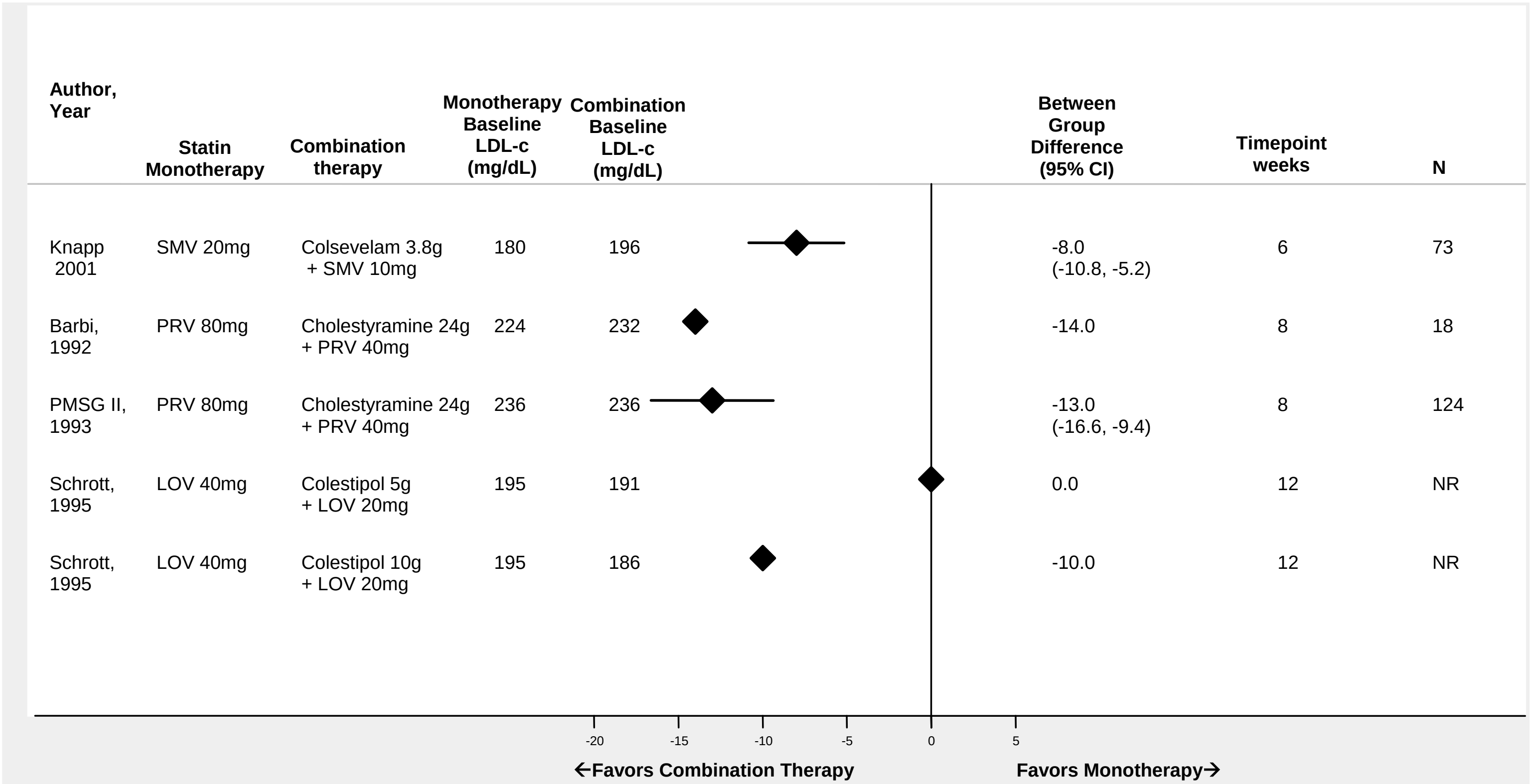
ATV atrovastatin; SMV simvastatin; NR not reported
For diamonds without confidence intervals, SE/SD could not be calculated

***Low* potency statin combination therapy versus *mid* potency statin monotherapy**

Four trials reported mean percent change in LDL-c (5 comparisons).[118-122] In four comparisons, the difference between combination therapy and statin monotherapy on lowering LDL-c ranged from 8 percent to 18 percent, favoring combination therapy. Duration of therapy ranged from 6-12 weeks. One trial that used a lower dose of colestipol with statin in one of its combination arms found no difference between combination therapy and statin monotherapy at lowering LDL-c, which may have contributed to the lack of significant difference in this comparison.[122]

The results of almost all comparisons favored low potency statin in combination with bile acid sequestrant for lowering LDL-c. We graded the strength of evidence as moderate (Table 8). Only two trials reported or provided sufficient information for us to calculate SE for the LDL-c difference in differences, and therefore, we did not perform meta-analyses (Figure 4).

Figure 4: Mean difference in percent LDL change from baseline to time point comparing low potency combination therapy with bile acid sequestrants to mid potency statin monotherapy



LOV lovastatin; PRV pravastatin; SMV simvastatin; NR not reported
For diamonds without confidence intervals, SE/SD could not be calculated

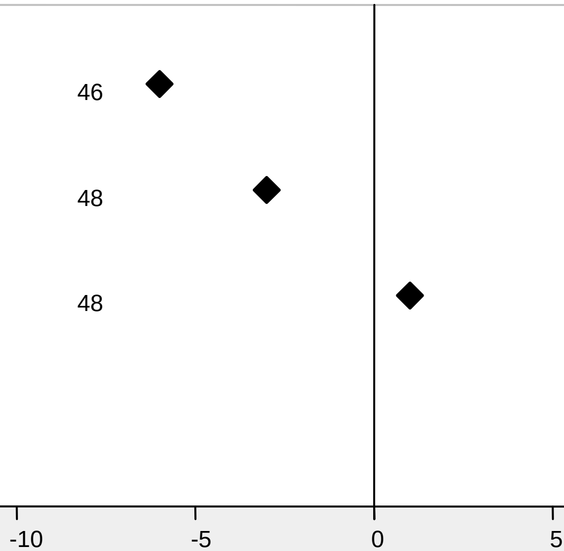
HDL-c

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**

Two trials reported on mean percent change in HDL-c.[86,87] At 4 weeks, one trial found that combination therapy raised HDL-c 6 percent more than monotherapy.[86] At 12 weeks, the other trial showed that combination therapy with colestipol 5g + simvastatin 20mg raised HDL-c 3 percent more than statin monotherapy. However, the other combination arm in this trial, which used a higher dose of colestipol (10g) in combination with simvastatin 20mg, was less effective than statin monotherapy at raising HDL-c (between group difference 1 percent that favored monotherapy). Overall, the results showed inconsistent effects on raising HDL-c,(Figure 5) we graded the strength of evidence as insufficient (Table 7).

Figure 5: Mean difference in percent HDL change from baseline to time point comparing mid potency combination therapy with bile acid sequestrants to high potency statin monotherapy

Author, Year	Statin Monotherapy	Combination therapy	Monotherapy Baseline HDL-c (mg/dL)	Combination Baseline HDL-c (mg/dL)	Between Group Difference (95% CI)	Timepoint weeks	N
Hunninghake, 2001	ATV 80mg	Colsevelam 3.8g + ATV 10mg	47	46	-6.0	4	38
Johansson, 1995	SMV 40mg	Colestipol 5g + SMV 20mg	51	48	-3.0	12	55
Johansson, 1995	SMV 40mg	Colestipol 10g + SMV 20mg	51	48	1.0	12	54



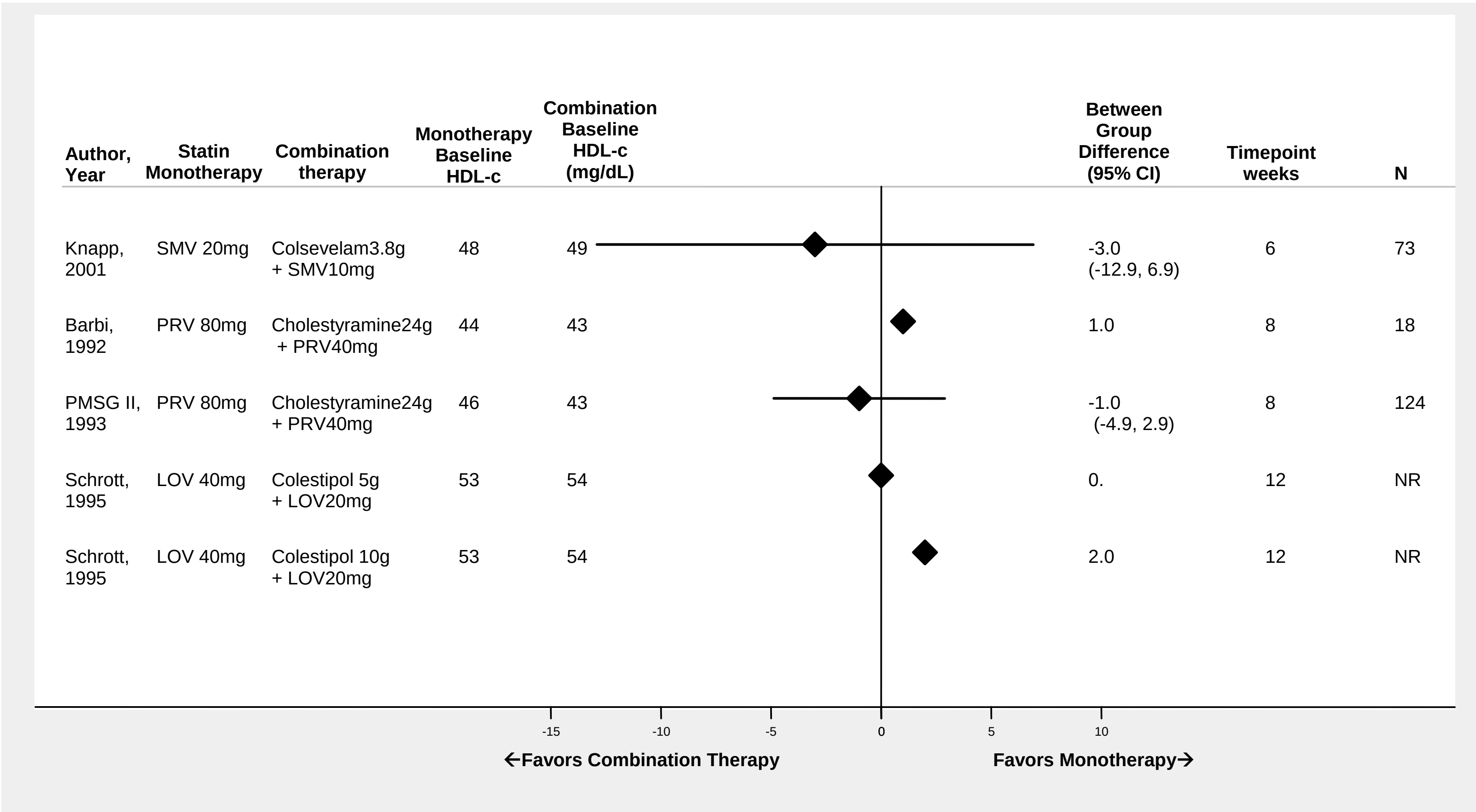
←Favors Combination Therapy   Favors Monotherapy→

ATV atorvastatin; SMV simvastatin;
For diamonds without confidence intervals, SE/SD could not be calculated

***Low* potency statin combination therapy versus *mid* potency statin monotherapy**

Four trials reported on mean percent change in HDL-c. In these trials,[118-122] the effects on raising HDL-c were inconsistent and showed little to no absolute difference between combination therapy and statin monotherapy (range 2 percent difference in favor of monotherapy to 5 percent difference in favor of combination therapy). Duration of therapy ranged from 6-12 weeks. We graded the strength of evidence as insufficient (Table 8). Only two trials reported or provided sufficient information for us to calculate SE for the LDL-c difference in differences, and therefore, we did not perform meta-analyses (Figure 6).

Figure 6: Mean difference in percent HDL change from baseline to time point comparing low potency combination therapy with bile acid sequestrants to high potency statin monotherapy



LOV lovastatin; PRV pravastatin; SMV simvastatin; NR not reported
For diamonds without confidence intervals, SE/SD could not be calculated

Total Cholesterol:HDL

No studies reported on total cholesterol:HDL ratio.

Atherosclerosis

No studies reported on atherosclerosis.

Adherence

Mid potency statin combination therapy versus high potency statin monotherapy

One trial reported on treatment adherence,[86] which was assessed with a pill count at 4 weeks. In the statin monotherapy arm, adherence was 88 percent and was 91 percent in the combination arm.

Low potency statin combination therapy versus mid potency statin monotherapy

One trial reported on treatment adherence.[122] Adherence to medications was 95 percent in the statin monotherapy arm and 93 percent in the combination arm at 12 weeks. The authors did not describe how adherence with medication was assessed.

Any Adverse Event

No studies reported on the occurrence of any adverse events.

Withdrawal due to Adverse Events

Mid potency statin combination therapy versus high potency statin monotherapy

One trial reported on withdrawals due to adverse events.[86] Both the statin monotherapy arm and the combination therapy arm had one person withdraw.

Low potency statin combination therapy versus mid potency statin monotherapy

Only one trial reported the number of participants who withdrew from the study due to an adverse event.[121] At 6 weeks, no participants in the monotherapy arm had withdrawn, while 1 participant in the combination arm withdrew due to an adverse event.

Cancer

No studies reported on cancer.

Elevated Liver Transaminases

Mid potency statin combination therapy versus high potency statin monotherapy

One trial reported on withdrawals due to elevated liver transaminases.[86] No significant elevations of AST and/or ALT >3 times the upper limit of normal occurred in either arm.

Low potency statin combination therapy versus mid potency statin monotherapy

No studies reported elevated liver transaminases.

Adverse Musculoskeletal Events

No studies reported on adverse musculoskeletal events such as elevated CPK, myalgia or rhabodomyolysis.

New Onset Diabetes Mellitus

No studies reported on any diabetes-related outcomes.

Subgroups of patients (KQ3)

No study reported on the comparative effectiveness of bile acid sequestrant plus statin on benefits or harms as compared to intensification of statin monotherapy among subgroups.

Table 7: Mid potency statin combination therapy with bile acid sequestrants as compared to high potency statin monotherapy: strength of evidence

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other issues	Findings and Magnitude of Effect	Strength of Evidence
Long Term Benefits and Serious Adverse Events								
Mortality	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Acute Coronary Events	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Serious Adverse Events	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Surrogate Clinical Outcomes								
LDL-c	2 (122)	Medium [1 trial with Jadad score<3]	Indirect [Calculated LDL in both trials]	Inconsistent [2 comparisons effect favors monotherapy, 1 comparison favors combination therapy]	Imprecise	Not detected None	Two studies with inconsistent results on LDL-c.	Insufficient
HDL-c	2 (122)	Medium [1 trial with Jadad score<3]	Direct [Measured HDL in both trials]	Inconsistent [2 comparisons effect favors combination therapy, 1 comparison favors monotherapy]	Imprecise	Not detected None	Two studies with inconsistent results on HDL-c.	Insufficient

HDL = high density lipoprotein; LDL= low density lipoprotein; NA =not applicable

Table 8: Low potency statin combination therapy with bile acid sequestrants as compared to mid potency statin monotherapy: strength of evidence

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long Term Benefits and Serious Adverse Events								
Mortality	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Acute Coronary Events	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Serious Adverse Events	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Surrogate Clinical Outcomes								
LDL-c	4 (288)	Medium [2 trials with Jadad score<3]	Indirect [Calculated LDL in all trials]	Consistent [4 comparisons favor combination therapy, 1 comparison no difference]	Imprecise	Not detected None	Studies favor low potency statin in combination with bile acid sequestrant by lowering LDL-c up to 14% more than mid potency statin monotherapy at 6-12 weeks.	Moderate
HDL-c	4 (288)	Medium [2 trials with Jadad score<3]	Direct [Measured HDL in all trials]	Inconsistent [2 comparisons favor combination, 2 comparisons favor monotherapy, 1 comparison no difference]	Imprecise	Not detected None	Four studies with inconsistent results on HDL-c.	Insufficient

HDL=high density lipoprotein; LDL=low density lipoprotein; NA= not applicable

Combined Lipid-Modifying Therapy with Statin and Ezetimibe versus Intensification of Statin Monotherapy

Study Characteristics

We included 38 trials (10,955 participants in eligible arms) that compared intensification of statin monotherapy to lower potency statin therapy in combination with ezetimibe. The 38 trials were reported 41 articles.[70-73 ,75-84 ,88-97 ,101-110 ,123 ,124 ,127-130 ,132] All studies were parallel arm RCTs, except one crossover RCT.[76] The studies were conducted in various geographic locations including Europe, Middle East, Asia, Latin America, North America, and some on multiple continents. Two trials did not report their location.[88 ,90] There were 14 single center trials[75-82 ,84 ,95 ,106 ,107 ,128 ,129], and 24 multicenter trials.[70-73 ,83 ,89 ,91-94 ,96 ,97 ,101 ,102 ,105 ,108 ,110 ,123 ,124 ,127 ,130] Most trials recruited patients with hyperlipidemia; [71-73 ,88 ,90 ,94 ,124 70 ,75-82 ,102 ,105 ,108 ,123 ,129]; however, several studies recruited only patients with preexisting CHD (n=13) [83 ,89 ,95-97 ,101 ,103 ,104 ,106 ,107 ,110 ,127 ,128 ,130] or patients with DM (n=5).[91-93 84 ,129] Treatment duration ranged from 4 to 24 weeks. Twelve studies compared high potency statin monotherapy to low potency statin in combination with ezetimibe among general populations of patients with hyperlipidemia[70-73 75-82]; while there was one study that evaluated this comparison among patients with preexisiting CHD [83] and one study that evaluated this comparison among patients with DM.[84] Twelve studies compared high potency statin monotherapy to mid potency statin in combination with ezetimibe among general populations of patients with hyperlipidemia;[70-73 ,88 ,90 ,94 ,97 ,102 ,103 ,105 ,108 ,110] while 10 studies evaluated this comparison among patients with preexisiting CHD[83 ,89 ,95 ,96 ,101 ,104 ,106 ,107 ,127 ,128] and 3 studies evaluated this comparison among patients with DM. [91-93 ,109 ,132] Finally, 7 studies compared mid potency statin monotherapy to low potency statin in combination with ezetimibe among general populations with hyperlipidemia;[70-73 ,81 ,123 ,124] while 2 studies evaluated this comparison among patients with preexisiting CHD [83 ,130] and one study evaluated this comparison among patients with DM.[129] (Appendix E Evidence Tables)

Population Characteristics

Most participants were in their 50s-60s.[70-73 ,88-97 ,123 ,124 75-82 ,84 ,101-110 ,127-129 ,132] Two studies had participants whose mean age was in the 70s.[83 ,130] One trial reported a significant between group difference with respect to age, where the combination therapy arm was significantly older (p=0.04).[84] Female participants varied between trials, ranging from 12 percent to 70 percent. One study had only men.[75] Race was reported in most trials, and the majority were white (56 percent to 96 percent), with black, Hispanic, and Asian participants the next most common groups. Smoking status was reported in less than half of studies (n=17), and current smoking status varied between studies (range 6 percent to 69 percent).[72 ,88 ,94 ,95 ,97 ,124 77-83 ,104 ,106 ,107 ,130] Some trials included only diabetics (n=5)[84 ,91-93 ,129]and other trials had no diabetics (n=2).[75 ,81] DM status was reported in 21 other trials, and ranged from 2 percent to 67 percent of participants.[88 ,89 ,94-97 ,123 ,124 77-79 ,83 ,84 ,104-108 ,110 ,128 ,130] Prior CHD and revascularization events were not consistently reported across trials.

Interventions

Fourteen studies compared high potency statin monotherapy to low potency statin in combination with ezetimibe.[70-73 75-84] The statin monotherapy regimens included simvastatin, rosuvastatin, and atorvastatin. The combination therapy regimens included simvastatin and atorvastatin in combination with ezetimibe. Twenty-five studies compared high potency statin monotherapy to mid potency statin in combination with ezetimibe.[70-73, 88-97, 109, 132, 83, 101-108, 110, 127, 128] The monotherapy regimens included simvastatin, rosuvastatin, and atorvastatin. The combination therapy included rosuvastatin, simvastatin and atorvastatin in combination with ezetimibe. Ten studies compared mid potency statin monotherapy to low potency statin in combination with ezetimibe.[70-73, 81, 83, 123, 124, 129, 130] The monotherapy regimens included simvastatin, rosuvastatin, fluvastatin and atorvastatin. The combination therapy included simvastatin, rosuvastatin, fluvastatin, lovastatin and atorvastatin in combination with ezetimibe.

Outcomes

Key Points

- **Long-Term Benefits**
    - There is insufficient evidence to compare the long-term benefits of combined lipid-modifying therapy with ezetimibe and statin to intensification of statin monotherapy at all potency levels.
- **Serious Adverse Events**
    - Fewer serious adverse events occur with high potency statin monotherapy as compared to a mid potency statin with ezetimibe (SOE: high). There is insufficient evidence within other potency comparisons.
- **Surrogate Outcomes**
    - A low potency statin combined with ezetimibe is more effective than high potency statin monotherapy for lowering LDL-c (SOE: low).
    - A mid potency statin combined with ezetimibe is more effective than high potency statin monotherapy for lowering LDL-c (SOE: moderate).
    - A low potency statin combined with ezetimibe is more effective than mid potency statin monotherapy for lowering LDL-c (SOE: moderate).
    - A low potency statin combined with ezetimibe is more effective than high potency statin monotherapy for raising HDL-c (SOE: low).
    - A mid potency statin combined with ezetimibe is more effective than high potency statin monotherapy for raising HDL-c (SOE: low).
    - A low potency statin combined with ezetimibe is more effective than mid potency statin monotherapy for raising HDL-c (SOE: low).
- **Short-Term Side Effects**
    - There is insufficient evidence to compare the rates of adverse events between combined lipid-modifying therapy with ezetimibe and statin compared with intensification of statin monotherapy at any potency level.
    - There is insufficient evidence to compare the rates of elevated liver transaminases between combined lipid-modifying therapy with ezetimibe and statin compared with intensification of statin monotherapy at any potency level.
    - There is insufficient evidence to compare the rates of adverse musculoskeletal events between combined lipid-modifying therapy with ezetimibe and statin compared with intensification of statin monotherapy at any potency level
- **Adherence**

- There is insufficient evidence to compare medication adherence between combined lipid-modifying therapy with ezetimibe and statin to intensification of statin monotherapy at all potency levels.

- **Subgroups**
  - CHD
    - Harms:
      - There is insufficient evidence to compare the harms of combined lipid-modifying therapy with ezetimibe and statin to intensification of statin monotherapy at any statin potencies among the CHD subgroup.
    - Benefits:
      - A mid potency statin combined with ezetimibe is more effective than high potency statin monotherapy for lowering LDL-c among CHD patients (SOE: moderate). There is insufficient evidence within other potency comparisons.
      - A mid potency statin combined with ezetimibe is more effective than high potency statin monotherapy for raising HDL-c among CHD patients (SOE: low). There is insufficient evidence within other potency comparisons.
  - DM
    - Harms:
      - There is insufficient evidence to compare the harms of combined lipid-modifying therapy with ezetimibe and statin to intensification of statin monotherapy at any statin potencies among the DM subgroup.
    - Benefits
      - A mid potency statin with ezetimibe is more effective than High potency statin monotherapy for lowering LDL-c among DM patients (SOE: moderate). There is insufficient evidence within other potency comparisons.
      - A mid potency statin combined with ezetimibe is more effective than high potency statin monotherapy for raising HDL-c among DM patients (SOE: moderate). There is insufficient evidence within other potency comparisons.

Long-term benefits and serious adverse events (KQ1)

Mortality

***Low* potency statin combination therapy versus *high* potency statin monotherapy**

Two studies reported mortality.[71,72] In one trial, there was one death in the ezetimibe 10mg + simvastatin 20mg arm, and no deaths in any other arm.[71] In the other trial, there was one death in the ezetimibe 10mg + simvastatin 20mg arm, and no deaths reported in other arms.[72] We graded the strength of evidence as insufficient.

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**

Seven studies reported mortality. [71,72,90,102,103,105,108,110] Overall, mortality was very low with very few deaths. Monotherapy was favored in the studies that showed a difference between treatments; however, the between-group differences were not statistically significant (Table 9). Given the limited number of events, we are unable to compare the effect between groups and have graded the evidence as insufficient.

Table 9: Proportion of deaths in each arm of <u>mid</u> potency statin combination therapy versus <u>high</u> potency statin monotherapy

Author, year	Regimen	Proportion of deaths, monotherapy arm	Proportion of deaths, combination therapy arm
Bays 2011 [102]	R20 v R10/E10	0	0
Zieve 2010[103], Ben-Yehuda 2011 [110]	A40 v A10/E10	<1	<1
Foody 2010 [105]	A40 v S20/E10	0.4	0.4
Foody 2010 [105]	A20 v S20/E10	0	0.4
Robinson 2009 [108]	A40 v S20/E10	0	0
Robinson 2009 [108]	A20 v S20/E10	0	0
Bays 2004 [71]	A80 v S20/E10	0	NR*
Bays 2004 [71]	S40 v S20/E10	0	NR*
Davidson 2002 [72]	S80 v S20/E10	NR	1.72
Davidson 2002 [72]	S40 v S20/E10	NR	1.72
Catapano 2006 [90]	R40 v S20/E10	0	0
Catapano 2006 [90]	R40 v S20/E10	0	0

*1 death in this arm but cannot calculate proportion; NR not recorded; A atorvastatin; R rosuvastatin; S simvastatin; E ezetimibe

<u>Low</u> potency statin combination therapy versus <u>mid</u> potency statin monotherapy

Two studies reported mortality.[71,72] No deaths occurred in eligible arms in either trial. We graded the strength of evidence as insufficient.

Acute Coronary Events

<u>Low</u> potency statin combination therapy versus <u>high</u> potency statin monotherapy

No studies reported on acute coronary events.

<u>Mid</u> potency statin combination therapy versus <u>high</u> potency statin monotherapy

One study reported on acute coronary events. [97] There was one fatal MI reported in the combination arm of that study (ezetimibe 10mg + atorvastatin 10mg). There were no fatal MIs reported in the monotherapy arm. We graded the strength of evidence as insufficient.

<u>Low</u> potency statin combination therapy versus <u>mid</u> potency statin monotherapy

No studies reported on acute coronary events.

Cerebrovascular Disease

No studies reported on cerebrovascular events.

Revascularization Procedures

No studies reported on revascularization events.

Serious Adverse Events

***<u>Low</u>* potency statin combination therapy versus *<u>high</u>* potency statin monotherapy**
No studies reported on serious adverse events.

***<u>Mid</u>* potency statin combination therapy versus *<u>high</u>* potency statin monotherapy**

Three studies reported serious adverse events.[97 103 ,105 ,110] Two studies favored monotherapy, although the absolute difference between arms was small (range 1 percent to 2 percent difference favoring monotherapy). One study showed no difference between monotherapy and combination therapy.[103 ,110] We graded the strength of evidence as high.

***<u>Low</u>* potency statin combination therapy versus *<u>mid</u>* potency statin monotherapy**

One study reported serious adverse events.[123] The monotherapy arm had 3 percent lower proportion of serious adverse events than the combination therapy group, although the individual rates were low overall (8% in combination therapy, and 5% in monotherapy). We graded the strength of evidence as insufficient.

Surrogate outcomes, short-term side effects and adherence (KQ2)

Almost all included RCTs evaluated surrogate outcomes including LDL-c and HDL-c. In several RCTs, medication adherence and short-term side effects were evaluated including elevated liver transaminases and elevated creatinine phosphokinase. We identified no eligible non-randomized extensions of RCTs or FDA reports.

LDL-c

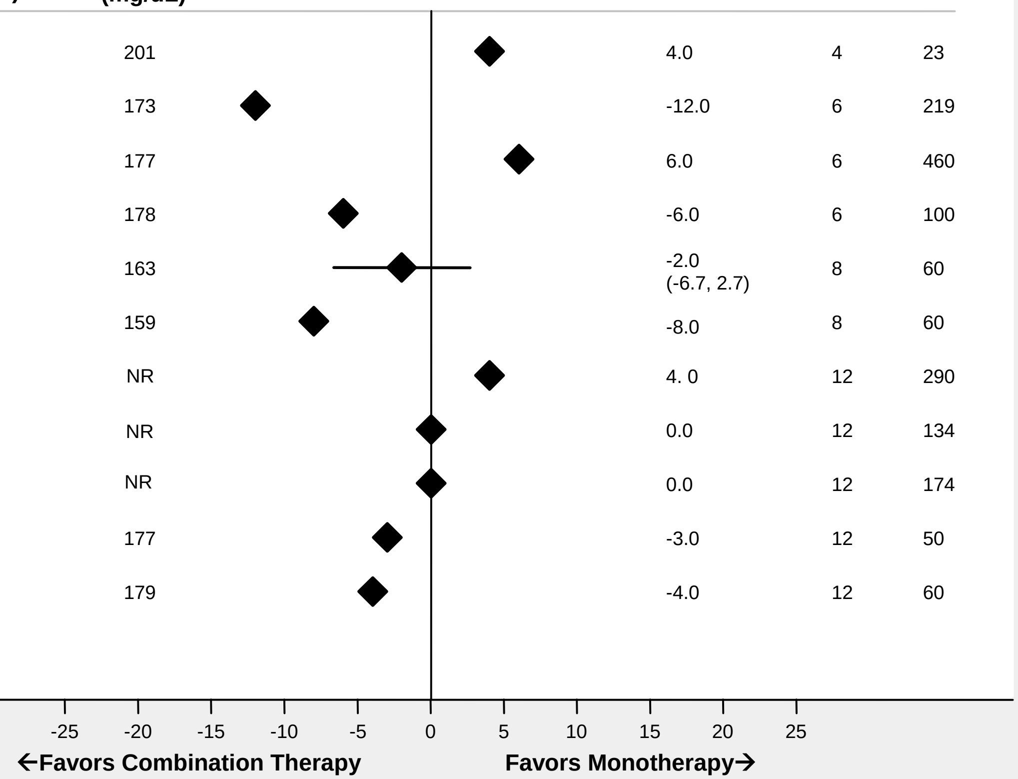
***<u>Low</u>* potency statin combination therapy versus *<u>high</u>* potency statin monotherapy**

Twelve studies evaluated LDL-c outcomes, with some trials reporting on multiple eligible arms for this potency comparison (17 arms).[70-73 75-82] Duration of therapy ranged from 6-12 weeks. As shown in Figure 7, six comparisons favored combination therapy for lowering LDL-c as compared to monotherapy (difference 2 percent to 12 percent). [75 ,77 ,79-82] Three comparisons favored monotherapy (difference 4 percent to 6 percent) [70 ,71 ,76]and three showed no difference. [72 ,73 ,78] Four studies had multiple arms comparing low potency statin combination therapy with different doses of high potency statin monotherapy. [70-73] Only the highest dose of statin monotherapy is shown in the figure. Of the other comparison arms, four out of five favored combination therapy (difference 3.4 percent to 8 percent). [71-73] One comparison favored monotherapy (difference 1.2 percent).[70] No studies reported LDL-c goal attainment.

The results of six out of twelve studies favored low potency statin in combination with ezetimibe for lowering LDL-c (Figure 7). We graded the strength of evidence as low. Summary estimates from meta-analysis are not reported due to high heterogeneity (I^2=100%).

Figure 7: Mean difference in percent LDL change from baseline to time point comparing low potency combination therapy with ezetimibe to high potency monotherapy

Author, Year	Statin Monotherapy	Combination Therapy	Monotherapy Baseline LDL-c (mg/dL)	Combination Baseline LDL-c (mg/dL)	Between Group Difference (95% CI)	Timepoint weeks	N
Araujo 2010	SMV 80mg	Ezetimibe 10mg +SMV10	206	201	4.0	4	23
Ahmed 2008	ATV 20mg	Ezeimitibe 10mg +SMV 10	173	173	-12.0	6	219
Ballantyne 2005	ATV 80mg	Ezetimibe10mg +SMV 10mg	183	177	6.0	6	460
Florentin 2011	SMV 40mg	Ezetimibe 10mg +SMV10	172	178	-6.0	6	100
Lee 2011	ATV 20mg	Ezetimibe 5mg +ATV 5mg	164	163	-2.0 (-6.7, 2.7)	8	60
Lee 2012	ATV 20mg	Ezetimibe 5mg +ATV 5mg	161	159	-8.0	8	60
Bays 2004	SMV 80mg	Ezetimibe 10mg +SMV 10mg	NR	NR	4. 0	12	290
Davidson 2002	SMV 80mg	Ezetimibe 10mg +SMV 10mg	NR	NR	0.0	12	134
Goldberg 2004	SMV 80mg	Ezetimibe 10mg +SMV 10mg	NR	NR	0.0	12	174
Liberopoulos 2013	SMV 40mg	Ezetimibe 10mg +SMV 10mg	176	177	-3.0	12	50
Moutzouri 2012	SMV 80mg	Ezetimibe 10mg +SMV 10mg	174	179	-4.0	12	60



ATV atorvastatin; SMV simvastatin; NR not reported
For diamonds without confidence intervals, SE/SD could not be calculated

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**

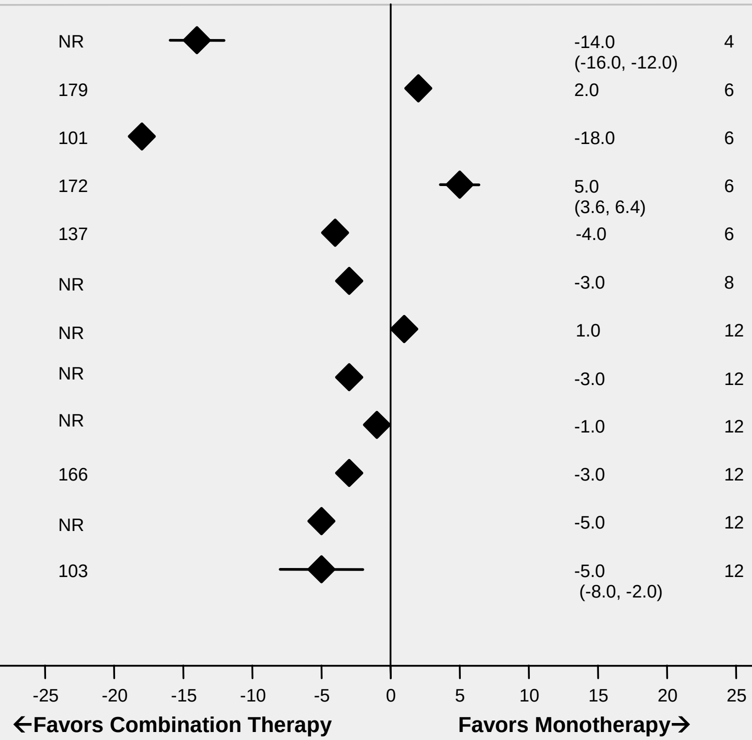
Eleven studies evaluated LDL-c outcomes with some trials reporting on multiple eligible arms for this potency comparison (22 arms).[70-73 ,88 ,90 ,94 ,97 ,102 ,103 ,105 ,108 110] As shown in Figure 8, eight comparisons favored combination therapy for lowering LDL-c as compared to monotherapy (difference 3% to 18%). [71 ,73 ,88 ,94 ,97 ,102 ,103 ,105 ,108 ,110] Duration of therapy ranged from 4-12 weeks. Two comparisons favored monotherapy (difference 2% to 5%). [70 ,90] and two comparisons were neutral. [72 ,88] Eight studies had multiple arms comparing mid potency statin combination therapy with different doses of high potency statin monotherapy. [70-73 ,88 ,90 ,105 ,108] Only the highest dose of statin monotherapy is shown in the figure 7. Of the other comparison arms, eight out of ten favored combination therapy (difference 2.3% to 14%) [70 ,71 ,73 ,88 ,105 ,108], one favored monotherapy (difference 5.2%) [90] and the other was neutral (0.8% difference).[72] In addition, 5 studies (7 comparisons) reported on attainment of ATP III LDL-c goals. [102 ,103 ,105 ,108 ,110 104] In six comparisons, more patients in the combination therapy group achieved LDL target (difference 10.1% to 32.2%). [102 ,103 ,105 ,108 ,110] In one comparison, more patients in the monotherapy group achieved LDL target (difference 3%).[104]

The results of eight studies favored mid potency statin in combination with ezetimibe for lowering LDL-c (Figure 8). We graded the strength of evidence as moderate. Meta-analysis is not reported due to significant heterogeneity (I^2=100%)

.

Figure 8: Mean difference in percent LDL change from baseline to time point comparing mid potency combination therapy with ezetimibe to high potency monotherapy

Author, Year	Statin Monotherapy	Combination Therapy	Monotherapy Baseline LDL-c (mg/dL)	Combination Baseline LDL-c (mg/dL)	Between Group Difference (95% CI)	Timepoint weeks	N
Stein, 2004	ATV 20mg	Ezetimibe10mg +ATV10mg	NR	NR	-14.0 (-16.0, -12.0)	4	596
Ballantyne, 2005	ATV 80mg	Ezetimibe10mg +SMV20	183	179	2.0	6	463
Bays, 2011	RSV 20mg	Ezetimibe10mg +RSV10mg	102	101	-18.0	6	220
Catapano, 2006	RSV 40mg	Ezetimibe10mg +SMV20	173	172	5.0 (3.6, 6.4)	6	951
Robinson, 2009	ATV 40mg	Ezetimibe10mg +SMV20	140	137	-4.0	6	397
McKenney, 2007	RSV 20mg	Ezetimibe10mg +SMV20	NR	NR	-3.0	8	NR
Ballantyne, 2003	ATV 80mg	Ezetimibe10mg +ATV10mg	NR	NR	1.0	12	NR
Bays, 2004	SMV 80mg	Ezetimibe10mg +SMV20	NR	NR	-3.0	12	290
Davidson, 2002	SMV 80mg	Ezetimibe10mg +SMV20	NR	NR	-1.0	12	119
Foody, 2010	ATV 40mg	Ezetimibe10mg +SMV20	168	166	-3.0	12	NR
Goldberg, 2004	SMV 80mg	Ezetimibe10mg +SMV20	NR	NR	-5.0	12	173
Zieve 2010, Ben-Yehuda 2011	ATV 40mg	Ezetimibe10mg +ATV10mg	102	103	-5.0 (-8.0, -2.0)	12	1025



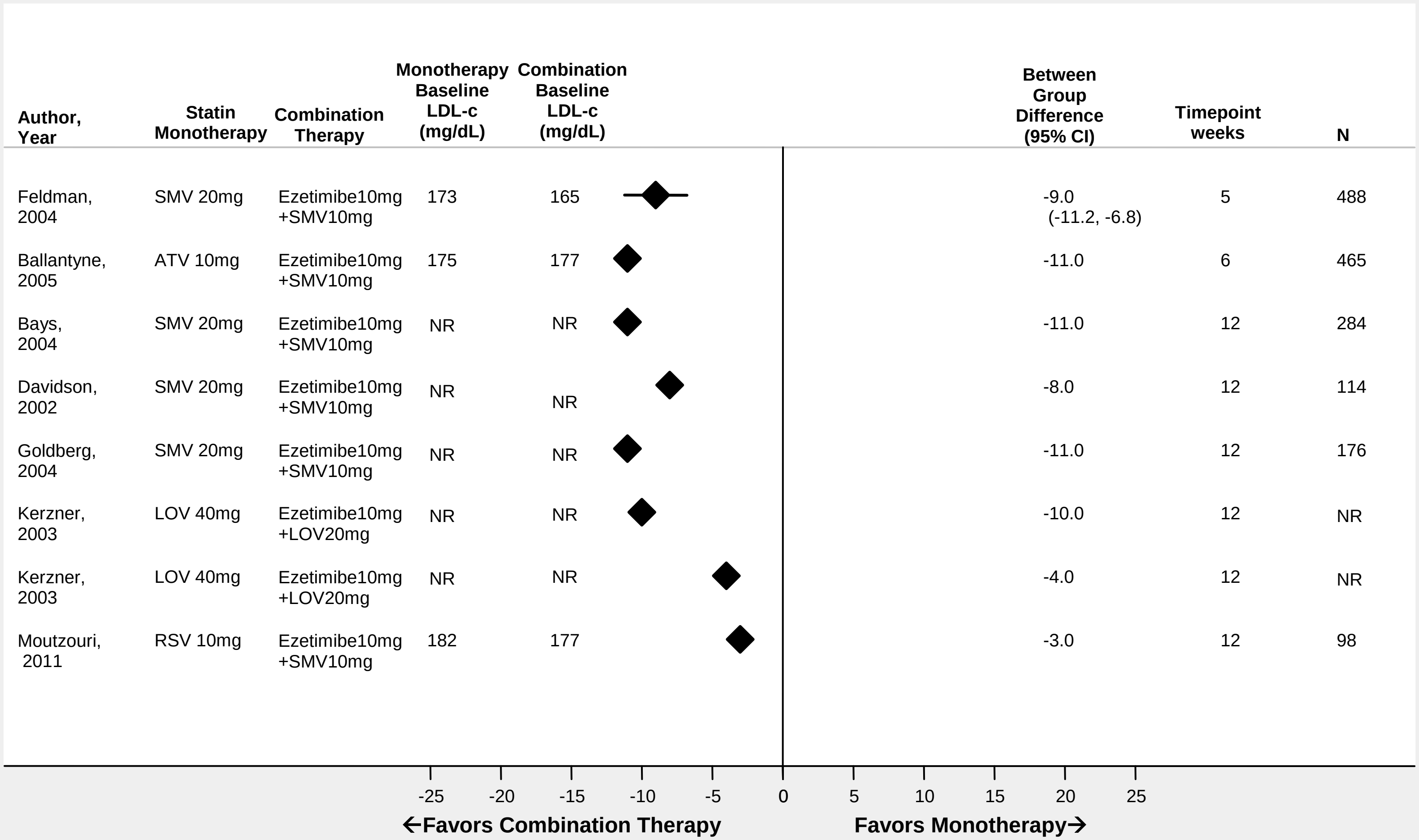
ATV= atorvastatin; SMV= simvastatin; NR= not reported
For diamonds without confidence intervals, SE/SD could not be calculated

<u>Low</u> potency statin combination therapy versus <u>mid</u> potency statin monotherapy

Seven studies evaluated LDL-c outcomes with some trials reporting on multiple eligible arms for this potency comparison (8 comparisons).[70-73,81,123,124] All comparisons favored combination therapy for lowering LDL-c as compared to monotherapy (difference 3% to 11.3%).[70-73,81,123,124] Duration of therapy ranged from 5-12 weeks. No studies reported LDL-c goal attainment.

The results of all studies favored mid potency statin in combination with ezetimibe for lowering LDL-c (Figure 9). We graded the strength of evidence as moderate. Meta-analysis of four studies [70,71,73,123] revealed a statistically significant difference between low potency statin combination therapy and mid potency statin monotherapy (pooled effect size = -11.0; 95% confidence interval [CI] -11.04 to -10.96), with low heterogeneity (I^2=4.2%).

Figure 9: Mean difference in percent LDL change from baseline to time point comparing low potency combination therapy with ezetimibe to mid potency monotherapy



Author, Year	Statin Monotherapy	Combination Therapy	Monotherapy Baseline LDL-c (mg/dL)	Combination Baseline LDL-c (mg/dL)	Between Group Difference (95% CI)	Timepoint weeks	N
Feldman, 2004	SMV 20mg	Ezetimibe10mg +SMV10mg	173	165	-9.0 (-11.2, -6.8)	5	488
Ballantyne, 2005	ATV 10mg	Ezetimibe10mg +SMV10mg	175	177	-11.0	6	465
Bays, 2004	SMV 20mg	Ezetimibe10mg +SMV10mg	NR	NR	-11.0	12	284
Davidson, 2002	SMV 20mg	Ezetimibe10mg +SMV10mg	NR	NR	-8.0	12	114
Goldberg, 2004	SMV 20mg	Ezetimibe10mg +SMV10mg	NR	NR	-11.0	12	176
Kerzner, 2003	LOV 40mg	Ezetimibe10mg +LOV20mg	NR	NR	-10.0	12	NR
Kerzner, 2003	LOV 40mg	Ezetimibe10mg +LOV20mg	NR	NR	-4.0	12	NR
Moutzouri, 2011	RSV 10mg	Ezetimibe10mg +SMV10mg	182	177	-3.0	12	98

ATV atorvastatin; LOV lovastatin; NR not reported; RSV rosuvastatin; SMV simvastatin;
For diamonds without confidence intervals, SE/SD could not be calculated

HDL-c

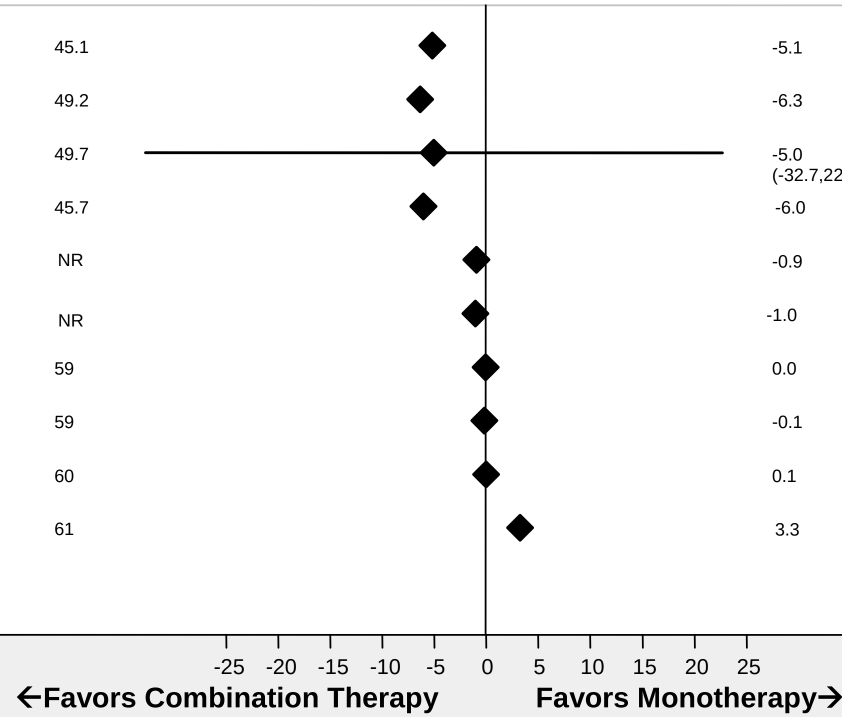
<u>Low</u> potency statin combination therapy versus <u>high</u> potency statin monotherapy

Ten studies (fourteen comparisons) evaluated HDL-c.[70-72,76-82] Shown in Figure 10, three comparisons favored combination therapy for raising HDL-c as compared to monotherapy (difference 5.14% to 6.3%). [76,79] Duration of therapy ranged from 4-12 weeks. Six comparisons were neutral [70-72,77,78,80] and one comparison favored monotherapy (difference 3.28%) [82] Three studies had multiple arms comparing low potency statin combination therapy with different doses of high potency statin monotherapy. [70-72] Only the highest dose of statin monotherapy is shown in the figure. Of the other comparison arms, three out of four favored combination therapy (difference 2.6% to 3.9%) [70,72] and one was neutral (0.5% difference). [71] [75]

The results of three studies favored low potency statin in combination with ezetimibe for raising HDL-c (Figure 10). We graded the strength of evidence as low (Table 11). Only two trials reported or provided sufficient information for us to calculate SE for the HDL-c difference in differences, and therefore, we did not perform meta-analysis.

Figure 10: Mean difference in percent HDL Change from baseline to time point comparing low potency combination therapy with ezetimibe to high potency monotherapy

Author, Year	Statin Monotherapy	Combination Therapy	Monotherapy Baseline HDL-c (mg/dL)	Combination Baseline HDL-c (mg/dL)	Between Group Difference (95% CI)	Timepoint weeks	N
Araujo 2010	SMV 80mg	Ezetimibe 10mg + SMV 10mg	44.7	45.1	-5.1	4	NR
Ballantyne 2005	SMV 80mg	Ezetimibe 10mg + SMV 10mg	48	49.2	-6.3	6	NR
Lee 2011	ATV 20mg	Ezetimibe 5mg + ATV 5mg	50.5	49.7	-5.0 (-32.7,22.7)	8	NR
Lee 2012	ATV 20mg	Ezetimibe 5mg + ATV 5mg	47.6	45.7	-6.0	8	NR
Bays 2004	SMV 80mg	Ezetimibe 10mg + SMV 10mg	NR	NR	-0.9	12	290
Davidson 2002	SMV 80mg	Ezetimibe 10mg + SMV 10mg	NR	NR	-1.0	12	NR
Florentin 2011	SMV 40mg	Ezetimibe 10mg + SMV 10mg	60	59	0.0	12	NR
Liberopoulos 2013	SMV 40mg	Ezetimibe 10mg + SMV 10mg	62	59	-0.1	12	NR
Moutzouri 2011	SMV 40mg	Ezetimibe 10mg + SMV 10mg	58	60	0.1	12	NR
Moutzouri 2012	SMV 80mg	Ezetimibe 10mg + SMV 10mg	60	61	3.3	12	NR



ATV atrovastatin; SMV simvastatin; NR not reported
For diamonds without confidence intervals, SE/SD could not be calculated

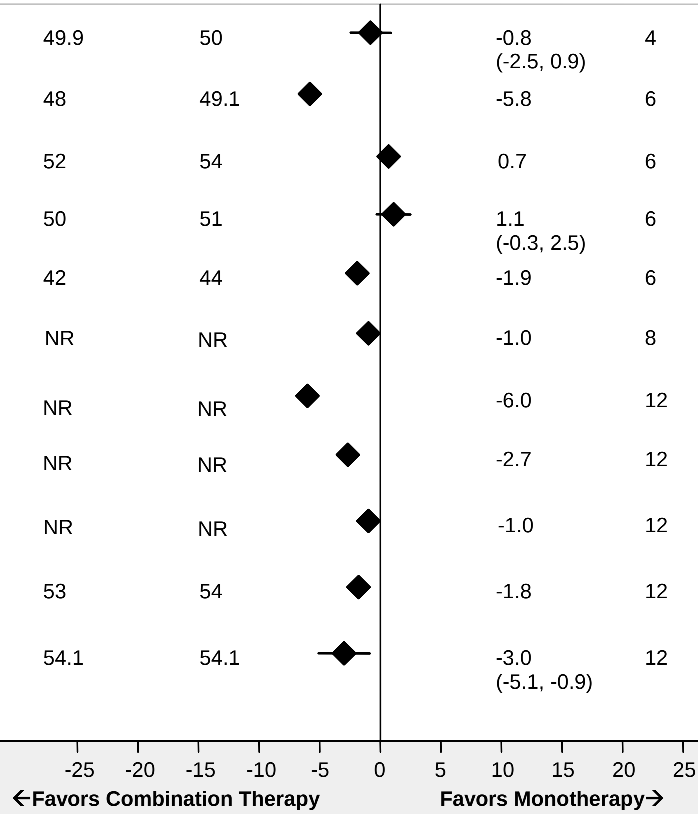
***Mid* potency statin combination therapy versus *high* potency statin monotherapy**

Eleven studies evaluated HDL-c.[70-73 ,88 ,90 ,94 ,97 ,102 ,103 ,105 ,108 ,110] Six studies favored combination therapy for raising HDL-c as compared to monotherapy (difference 1.8% to 6%). [70 ,71 ,73 ,88 ,103 ,105 ,108 ,110] Five studies were neutral. [97 ,102 72 ,90 ,94] Duration of therapy ranged from 4-12 weeks. Seven studies had multiple arms comparing low potency statin combination therapy with different doses of high potency statin monotherapy. [70 ,70 ,70-72 ,105 ,108] Only the highest dose of statin monotherapy is shown in the figure. Of the other comparison arms, seven out of nine favored combination therapy (difference 1.8% to 6%) [70 ,70 ,70-72] and two were neutral (difference 0.8 percent to 1.1 percent).[105 ,108 75]

The results of six studies favored mid potency statin in combination with ezetimibe for raising HDL-c (Figure 11). We graded the strength of evidence as low (Table 12). Summary estimates from meta-analysis are not reported due to high heterogeneity (I^2=81.1%).

Figure 11: Mean difference in percent HDL change from baseline to time point comparing mid potency combination therapy with ezetimibe to high potency statin monotherapy

Author, Year	Statin Monotherapy	Combination Therapy	Monotherapy Baseline HDL-c (mg/dL)	Combination Baseline HDL-c (mg/dL)	Between Group Difference (95% CI)	Timepoint weeks	N
Stein, 2004	ATV 20mg	Ezetimibe 10mg + ATV 10mg	49.9	50	-0.8 (-2.5, 0.9)	4	596
Ballantyne, 2005	ATV 80mg	Ezetimibe 10mg + SMV 20mg	48	49.1	-5.8	6	463
Bays, 2011	RSV 20mg	Ezetimibe 10mg + RSV 10mg	52	54	0.7	6	NR
Catapano, 2006	RSV 40mg	Ezetimibe 10mg + SMV 20mg	50	51	1.1 (-0.3, 2.5)	6	951
Robinson, 2009	ATV 40mg	Ezetimibe 10mg + SMV 20mg	42	44	-1.9	6	436
McKenney, 2007	RSV 20mg	Ezetimibe 10mg + SMV 20mg	NR	NR	-1.0	8	NR
Ballantyne, 2003	ATV 80mg	Avostatin 10mg +EZE 10mg	NR	NR	-6.0	12	NR
Bays, 2004	SMV 80mg	Ezetimibe 10mg + SMV 20mg	NR	NR	-2.7	12	NR
Davidson, 2002	SMV 80mg	Ezetimibe 10mg + SMV 20mg	NR	NR	-1.0	12	119
Foody, 2010	ATV 40mg	Ezetimibe 10mg + SMV 20mg	53	54	-1.8	12	NR
Zieve, 2010 Ben-Yehuda, 2011	A20mg/ATV40mg	Avostatin10mg + EZE10mg	54.1	54.1	-3.0 (-5.1, -0.9)	12	217



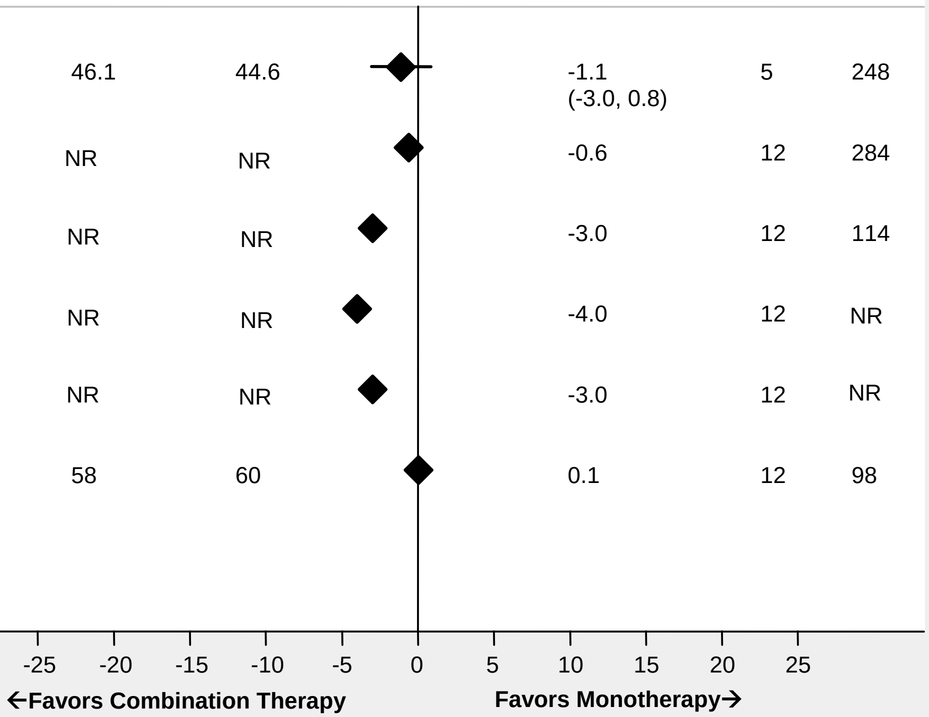
ATV atorvastatin; EZE ezetimibe; RSV rosuvastatin; SMV simvastatin; NR not reported
For diamonds without confidence intervals, SE/SD could not be calculated

<u>Low</u> potency statin combination therapy versus <u>mid</u> potency statin monotherapy

Five studies evaluated HDL-c.[71-73,81,123,124] Two studies (three comparisons) favored combination therapy for raising HDL-c as compared to monotherapy (difference 3% to 4%) (Figure 12).[72,124] Both comparisons in the Kersner et al study [124] were included in the figure because there were different low potency statin combination regimens used. Three studies were neutral (difference 0.05% to 1.1%).[71,81,123] We graded the strength of evidence as low (Table 13). Only one trial reported or provided sufficient information for us to calculate SE for the HDL-c difference in differences, and therefore, we did not perform meta-analyses.

Figure 12: Mean difference in percent HDL change from baseline to time point comparing low potency combination therapy with ezetimibe to mid potency statin monotherapy

Author, Year	Statin Monotherapy	Combination Therapy	Monotherapy Baseline HDL-c (mg/dL)	Combination Baseline HDL-c (mg/dL)	Between Group Difference (95% CI)	Timepoint weeks	N
Feldman, 2004	SMV 20	Ezetimibe 10mg +SMV10mg	46.1	44.6	-1.1 (-3.0, 0.8)	5	248
Bays, 2004	SMV 20	Ezetimibe 10mg +SMV10mg	NR	NR	-0.6	12	284
Davidson, 2002	SMV 20	Ezetimibe 10mg +SMV10mg	NR	NR	-3.0	12	114
Kersner, 2003	LOV 40	Ezetimibe 10mg + LOV 20mg	NR	NR	-4.0	12	NR
Kersner, 2003	LOV 40	Ezetimibe 10mg +LOV10mg	NR	NR	-3.0	12	NR
Moutzouri, 2011	RSV 10	Ezetimibe 10mg + SMV10mg	58	60	0.1	12	98



ATV atrovastatin; LOV lovastatin; SMV simvastatin; NR not reported
For diamonds without confidence intervals, SE/SD could not be calculated

Total Cholesterol:HDL

<u>Low</u> potency statin combination therapy versus <u>high</u> potency statin monotherapy

One study reported total cholesterol:HDL ratio.[71] The effects on lowering total cholesterol:HDL were inconsistent and showed little to no absolute difference between combination therapy and statin monotherapy.

<u>Mid</u> potency statin combination therapy versus <u>high</u> potency statin monotherapy

Eight studies (13 arms) reported total cholesterol:HDL ratio.[72,73,88,90,94,97,102,103,105,108,110] Most comparisons favored monotherapy for lowering total cholesterol:HDL as compared to combination therapy (difference 1.6% to 11.8%). .[72,73,88,94,97,102,103,105,108,110] Duration of therapy ranged from 6-12 weeks. However, two comparisons favored combination therapy (difference 1.1% to 4.2%).[90]

<u>Low</u> potency statin combination therapy versus <u>mid</u> potency statin monotherapy

No studies reported total cholesterol:HDL ratio.

Atherosclerosis

No studies reported on atherosclerosis

Adherence

<u>Low</u> potency statin combination therapy versus <u>high</u> potency statin monotherapy

No studies reported adherence.

<u>Mid</u> potency statin combination therapy versus <u>high</u> potency statin monotherapy

Two studies reported on adherence.[94,102] One study favored combination therapy with 98 percent adherence among combination therapy patients and 84 percent adherence among monotherapy patients (defined as returning 75 and 125% of dispensed tablets).[94] The other trial reported no difference in adherence between arms, with the majority of patients achieving >95 percent compliance with study therapy (study authors did not discuss in detail how compliance was assessed).[102]

<u>Low</u> potency statin combination therapy versus <u>mid</u> potency statin monotherapy

No studies reported adherence.

Any Adverse Event

<u>Low</u> potency statin combination therapy versus <u>high</u> potency statin monotherapy

No studies reported adverse events.

<u>Mid</u> potency statin combination therapy versus <u>high</u> potency statin monotherapy

Three studies reported adverse events.[97,103,105,110] In one comparison [103,110], more patients in the monotherapy arm experienced at least one adverse event (difference 3%). In three comparisons, more patients in the combination therapy arm experienced at least one adverse event (difference 2.5% to 5%). [97,105]

<u>Low</u> potency statin combination therapy versus <u>mid</u> potency statin monotherapy

One study reported adverse events.[123] More participants in the monotherapy group had an adverse event (66%) than the combination therapy group (56%) (p=0.02).

Withdrawal due to Adverse Events

***Low* potency statin combination therapy versus *high* potency statin monotherapy**

One study reported withdrawals due to adverse events.[72] In one monotherapy arm (simvastatin 40mg), 3 percent of patients withdrew due to adverse events. No participants in the combination arm or other monotherapy arm (simvastatin 80mg) withdrew due to adverse events.

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**

Five studies reported withdrawals due to adverse events (8 arms).[72,102,103,105,108,110] In one comparison, there was no difference in withdrawal due to adverse events between the combination therapy and monotherapy arms [72] with no event in either arm. In three comparisons, more patients in the combination therapy group withdrew due to adverse event (difference 1% to 2.3%).[103,105,110] In one comparison, more patients in the monotherapy group withdrew due to AE (difference 3.3 percent). [72]

***Low* potency statin combination therapy versus *mid* potency statin monotherapy**

Two studies reported withdrawals due to adverse events.[72,123] The combination arms in both studies had fewer withdrawals due to adverse events than the monotherapy arms (difference range 1% to 11% favoring combination therapy).

Cancer

No studies reported on cancer.

Elevated Liver Transaminases

***Low* potency statin combination therapy versus *high* potency statin monotherapy**

Two studies reported on elevated liver transaminases (AST and/or ALT > 3 times ULN).[78,79] No participants experienced elevated liver enzymes.

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**

Seven studies reported on elevated liver transaminases (AST and/or ALT > 3 times ULN). [90,94,97,102 103,105,108,110]Overall, few patients experienced elevated transaminases in any arm. In three comparisons, more patients in the combination therapy group experienced elevated liver transaminases (difference 0.2% to 1.4%).[90,94,105] In four comparisons, more patients in the monotherapy group experienced elevated liver transaminases (difference 0.7% to 1.8%). [97,105,108]

One comparison [90] (rosuvastatin 40 vs. simvastatin 20/ ezetimibe 10) showed no difference in the proportion of patients with elevated liver transaminases.

***Low* potency statin combination therapy versus *mid* potency statin monotherapy**

One study reported on elevated liver transaminases.[123] Overall, few patients experienced elevated transaminases in this trial (0% in monotherapy and 0.4% in combination therapy).

Musculoskeletal Adverse Events

***Low* potency statin combination therapy versus *high* potency statin monotherapy**

Two studies reported on CPK > 10 times ULN.[78,79] No patients in any eligible arm experienced CPK elevations. No studies reported on myalgia

Mid potency statin combination therapy versus high potency statin monotherapy

Seven studies reported on CPK > 10 times ULN. [90,94,97,102,103,105,108,110] Overall, few patients experienced CPK elevations regardless of treatment arm. In two comparisons, more patients in the combination therapy group experienced CPK > 10x ULN (difference 0.4% in both).[108] In two comparisons, more patients in the monotherapy group experienced CPK > 10x ULN (difference 0.1% to 0.3%).[97 90] Four comparisons showed no difference.[90,94,105] Three studies reported on myalgia.[90,97,103,110] There was little to no difference between treatment arms with respect to reports of myalgia (difference range 0% to 1%).

Low potency statin combination therapy versus mid potency statin monotherapy

One study reported on CPK > 10 times ULN.[123] No participants in the combination arm experienced CPK elevations, and only 1 percent of participants in the monotherapy arm had CPK elevations. No studies reported on myalgia.

New Onset Diabetes Mellitus

No studies reported on new-onset diabetes mellitus.

Acute Kidney Injury

No studies reported on acute kidney injury.

Subgroups of patients (KQ3)

There were many studies involving participants with DM and CHD. There were few studies making subgroup comparisons by gender (female), race (Black, Hispanic, and Asian), or age (> 75 years old). Surrogate clinical markers were commonly reported by subgroup, however, serious adverse events and mortality were not commonly reported by subgroup (Table 10).

Table 10: Summary of evidence available for subgroups comparing combination therapy with ezetimibe and statin to intensification of statin monotherapy

		Subgroup						
Outcomes	**Potency comparison**	**CHD # trials (#participants)**	**Diabetes mellitus # trials (#participants)**	**Females # trials (#participants)**	**Asian # trials (#participants)**	**Black # trials (#participants)**	**Hispanic # trials (#participants)**	**Elderly # trials (#participants)**
LDL-c	H v M	11 trials* (1792)	7 trials* 1328	2 trials* (547)	1 trial (NR)	2 trials* (28)	1 trial (52)	2 trials* (225)
	H v L	1 trial (84)	1 trial 21					
	M v L	2 trials* (87)	1 trial 24					
HDL-c	H v M	9 trials* (748)	6 trials 2741					1 trial (217)
	H v L	1 trial (84)	1 trial 21					
	M v L	2 trials* (87)	1 trial 24					
Non-HDL-c	H v M		3 trials (1366)					
	H v L							
	M v L							
Triglycerides	H v M		4 trials (1453)					
	H v L							
	M v L							
Total Cholesterol:HDL	H v M	1 trial (427)	2 trials (647)					1 trial (218)
	H v L							
	M v L							
LDL target attainment	H v M	4 trials* (590)	4 trials* (596)					1 trial (218)
	H v L							
	M v L							

		Subgroup						
Outcomes	**Potency comparison**	**CHD # trials (#participants)**	**Diabetes mellitus # trials (#participants)**	**Females # trials (#participants)**	**Asian # trials (#participants)**	**Black # trials (#participants)**	**Hispanic # trials (#participants)**	**Elderly # trials (#participants)**
Adherence	H v M		1 trial (537)					
	H v L							
	M v L							
Any adverse event	H v M	3 trials (632)	2 trials (653)					1trial (225)
	H v L							
	M v L							
Withdrawal due to adverse events	H v M	5 trials (774)	3 trials (1861)					1trial (225)
	H v L							
	M v L							
Serious adverse events	H v M							1trial (225)
	H v L							
	M v L							
Mortality	H v M							1trial (225)
	H v L							
	M v L							
Elevated liver transaminases	H v M	6 trials* (798)						1 trial (225)
	H v L							
	M v L							
Elevated CPK	H v M	4 trials (720)	1 trial (214)					1 trial (225)
	H v L							

		Subgroup						
Outcomes	**Potency comparison**	**CHD # trials (#participants)**	**Diabetes mellitus # trials (#participants)**	**Females # trials (#participants)**	**Asian # trials (#participants)**	**Black # trials (#participants)**	**Hispanic # trials (#participants)**	**Elderly # trials (#participants)**
	M v L							
Myalgia	H v M	1 trial (78)	2 trials (563)					
	H v L							
	M v L							

H v M= high potency monotherapy versus mid potency combination therapy; H v L= high potency monotherapy versus low potency combination therapy; M v L= mid potency monotherapy versus low potency combination therapy; CPK= creatinine phosphokinase; HDL= high density lipoprotein; LDL= low density lipoprotein

*means at least one of the trials did not report the number of participants, blank cell means no trial

Patients with Preexisting Coronary Heart Disease

Overall, 11 studies included analyses of patient populations with preexisiting CHD. One study compared low potency statin in combination with ezetimibe to high potency statin monotherapy among patients with preexisting CHD.[83] Ten studies compared mid potency statin in combination with ezetimibe to high potency statin monotherapy among patients with preexisiting CHD.[83,89,95,96,101,104,106,107,127,128]
Two studies compared low potency statin in combination with ezetimibe to mid potency statin monotherapy among patients with preexisting CHD.[83,130]

Mortality

Low potency statin combination therapy versus high potency statin monotherapy
No studies reported mortality among patients with preexisting CHD.

Mid potency statin combination therapy versus high potency statin monotherapy
Three studies reported mortality among patients with preexisting CHD.[89,96,127] No deaths occurred in these studies. We graded the strength of evidence as insufficient (Table 15).

Low potency statin combination therapy versus mid potency statin monotherapy
No studies reported mortality among patients with preexisting CHD.

Acute Coronary Events

Low potency statin combination therapy versus high potency statin monotherapy
No studies reported acute coronary events among patients with preexisting CHD.

Mid potency statin combination therapy versus high potency statin monotherapy
One study reported on acute coronary events, specifically fatal MI, among patients with preexisting CHD.[106] No fatal MI occurred in the monotherapy arm and one fatal MI occurred in the combination therapy arm. We graded the strength of evidence as insufficient (Table 15).

Low potency statin combination therapy versus mid potency statin monotherapy
No studies reported acute coronary events among patients with preexisting CHD.

Cerebrovascular Events

Low potency statin combination therapy versus high potency statin monotherapy
No study reported cerebrovascular events among patients with preexisting CHD.

Mid potency statin combination therapy versus high potency statin monotherapy
One study reported cerebrovascular events among patients with preexisting CHD, specifically transient ischemic attack (TIA).[127] One TIA occurred in the monotherapy arm (2%) and no events occurred in the combination arm, which was not a significant difference.

Low potency statin combination therapy versus mid potency statin monotherapy
No study reported cerebrovascular events among patients with preexisting CHD.

Revascularization Procedures

No studies reported on revascularization procedures among patients with preexisting CHD.

Serious Adverse Events

Low potency statin combination therapy versus high potency statin monotherapy
No study reported serious adverse events among patients with preexisting CHD.

Mid potency statin combination therapy versus high potency statin monotherapy
Three studies reported serious adverse events among patients with preexisting CHD.[89,101,127] Overall, the numbers of events were low. In two comparisons, more combination therapy patients experienced SAE (difference 0.02% to 1.4%).[89,101] In one comparison, more monotherapy group patients experienced SAE (difference 1.7 percent). We graded the strength of evidence as insufficient (Table 15).

Low potency statin combination therapy versus mid potency statin monotherapy
No study reported serious adverse events among patients with preexisting CHD.

LDL-c

Low potency statin combination therapy versus high potency statin monotherapy
One study reported on LDL-c outcomes among patients with preexisting CHD.[83] Combination therapy lowered LDL-c by 5 percent more than monotherapy. No studies reported LDL-c goal attainment. We graded the strength of evidence as insufficient (Table 14).

Mid potency statin combination therapy versus high potency statin monotherapy
Ten studies reported on LDL-c outcomes among patients with preexisting CHD.[83,89,95,96,101,104,106,107,127,128] In seven comparisons, combination therapy lowered LDL more than monotherapy (difference 5% to 15%).[83,89,95,96,101,127,128] Two studies were neutral (difference 1% to 3.1%)[104 107] and one study favored monotherapy.[106]

In addition, one study reported LDL-c change among female participants with preexisting CHD.[89] This study favored combination therapy for LDL-c reduction in female participants with CHD. Mean percent change in the monotherapy group was 21 percent, while mean percent change in the combination therapy group was 34 percent.

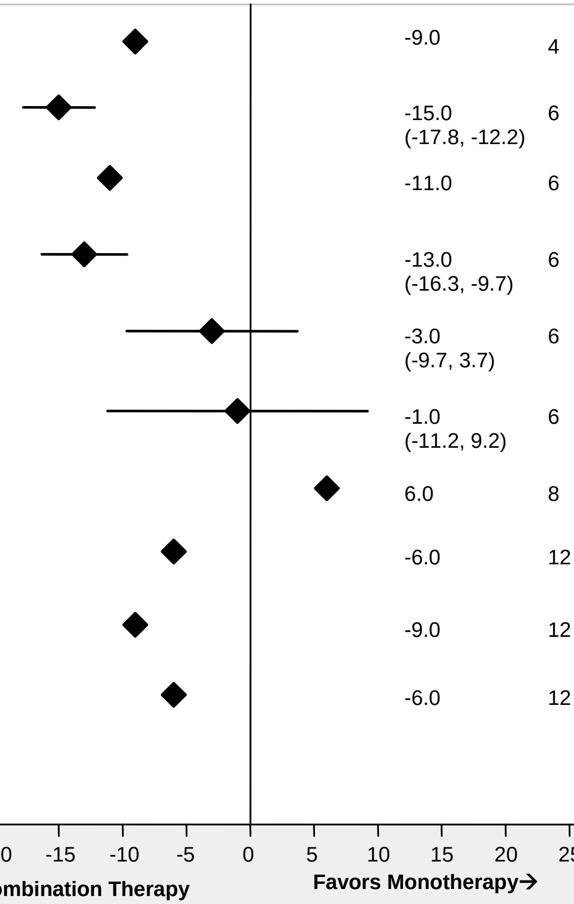
Four studies reported attainment of LDL-c < 100 mg/dL among patients with preexisting CHD.[89,95,96,127] Most comparisons favored combination therapy over monotherapy for attaining this LDL-c goal (difference range 13% to 49% favoring combination therapy), which as a statistically significant difference in 3 trials.[89,96,127]

The results of seven studies favored mid potency statin in combination with ezetimibe for lowering LDL-c among patients with preexisting CHD (Figure 13). We graded the strength of evidence as moderate (Table 15).

Summary estimates from meta-analysis are not reported due to high heterogeneity (I^2=91.5%).

Figure 13: Mean difference in percent LDL-c change from baseline to time point comparing mid potency combination therapy with ezetimibe to high potency monotherapy among CHD patients

Author, Year	Statin Monotherapy	Combination Therapy	Monotherapy Baseline LDL-c (mg/dL)	Combination Baseline LDL-c (mg/dL)	Between Group Difference (95% CI)	Timepoint, weeks	N
Piorkowski, 2006	ATV 40mg	Ezetimibe 10mg +ATV10mg	135	140	-9.0	4	51
Averna, 2010	SMV 40mg	Ezetimibe 10mg +SMV 20mg	128	126	-15.0 (-17.8, -12.2)	6	112
Bardini, 2010	SMV 40mg	Ezetimibe 10mg +SMV 20mg	124	128	-11.0	6	NR
Barrios, 2005	ATV 20mg	Ezetimibe 10mg +SMV 20mg	124	124	-13.0 (-16.3, -9.7)	6	422
Cho, 2010	ATV 20mg	Ezetimibe 10mg +SMV 20mg	132	134	-3.0 (-9.7, 3.7)	6	85
Pesaro, 2011	SMV 80mg	Ezetimibe 10mg +SMV 20mg	101	99	-1.0 (-11.2, 9.2)	6	78
Ostad, 2008	ATV 80mg	Ezetimibe 10mg +ATV 10mg	148	151	6.0	8	NR
Hamdan, 2011	ATV 20mg	Ezetimibe 10mg +ATV 10mg	131	124	-6.0	12	75
Okada, 2011	ATV 20mg	Ezetimibe 10mg +ATV 10mg	114	121	-9.0	12	78
Zieve, 2010 Ben-Yehuda, 2011 (Subgroup)	ATV 40mg	Ezetimibe10mg +ATV 10mg	NR	NR	-6.0	12	891



ATV atorvastatin; SMV simvastatin; NR not reported

For diamonds without confidence intervals, SE/SD could not be calculated

Low ***potency statin combination therapy versus mid potency statin monotherapy***

Two studies reported on LDL-c outcomes among patients with preexisting CHD.[83,130] Both trials favored combination therapy for LDL-c reduction (difference 1.6% to 8.3%). No studies reported LDL-c goal attainment. We graded the strength of evidence as insufficient (Table 16).

HDL-c

Low potency statin combination therapy versus high potency statin monotherapy

One study reported on HDL-c among patients with preexisting CHD.[83] Combination therapy raised HDL-c 9 percent more than monotherapy. We graded the strength of evidence as insufficient (Table 14).

Mid potency statin combination therapy versus high potency statin monotherapy

Nine studies reported HDL-c among patients with preexisting CHD.[89,95 83,101,104,106,107,127,128] One study favored combination therapy (difference 7.33%).[83] One study favored monotherapy (difference 6%).[128] However, most results were neutral (difference 0.1% to 5.6%, NS).[89,95 101,104,106,107,127]

The results were inconsistent with respect to raising HDL-c among patients with preexisting CHD (Figure 14). We graded the strength of evidence as low, given the inconsistent results (Table 15).

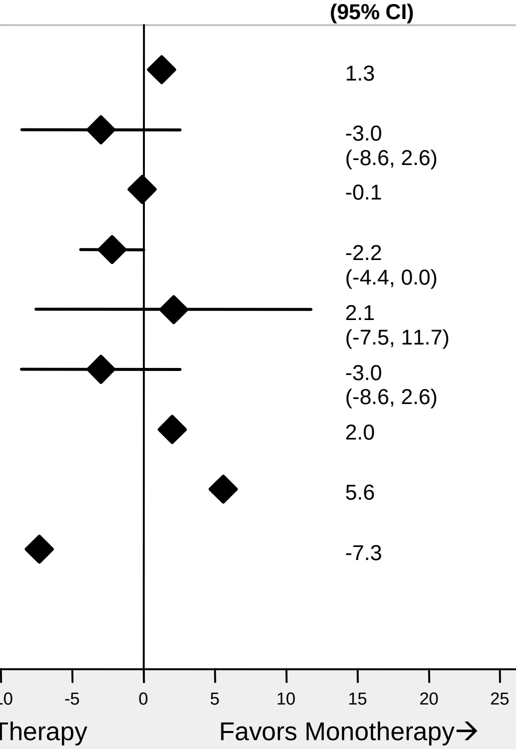
Meta-analysis is not reported due to high heterogeneity (I^2=94.0%).

Low potency statin combination therapy versus mid potency statin monotherapy

Two studies reported on HDL-c among patients with preexisting CHD.[83,130] One study favored combination therapy to increase HDL (difference 0.29%) while one study favored monotherapy to increase HDL (difference 7.71%). We graded the strength of evidence as insufficient (Table 16).

Figure 14: Mean difference in percent HDL change from baseline to time point comparing mid potency combination therapy with ezetimibe to high potency statin monotherapy in patients with CHD

Author, Year	Statin Monotherapy	Combination therapy	Monotherapy Baseline HDL-c (mg/dL)	Combination Baseline HDL-c (mg/dL)	Between Group Difference (95% CI)	Timepoint weeks	N
Piorkowski, 2007	ATV 40mg	Ezetimibe10mg + ATV10mg	50.7	53.8	1.3	4	51
Averna, 2010	SMV 40mg	Ezetimibe10mg + SMV10mg	48.8	50.5	-3.0 (-8.6, 2.6)	NR	NR
Bardini, 2010	SMV 40mg	Ezetimibe10mg + SMV20mg	NR	NR	-0.1	6	NR
Barrios, 2005	ATV 20mg	Ezetimibe10mg + SMV20mg	55.7	53.4	-2.2 (-4.4, 0.0)	6	422
Cho, 2010	ATV 20mg	Ezetimibe10mg + SMV20mg	46.1	45.2	2.1 (-7.5, 11.7)	6	85
Pesaro, 2011	SMV 80mg	Ezetimibe10mg + SMV20mg	45	42	-3.0 (-8.6, 2.6)	6	78
Ostad, 2008	ATV 80mg	Ezetimibe10mg + ATV10mg	52	58	2.0	8	NR
Hamdan, 2011	ATV 20mg	Ezetimibe10mg + ATV10mg	34.8	34.8	5.6	12	34
Okada, 2011	ATV 20mg	Ezetimibe10mg + ATV10mg	50.9	52.9	-7.3	12	78



ATV atorvastatin; SMV simvastatin; NR not reported
For diamonds without confidence intervals, SE/SD could not be calculated

Total Cholesterol:HDL

***Low* potency statin combination therapy versus *high* potency statin monotherapy**

No study reported total cholesterol: HDL ratio among patients with preexisting CHD.

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**

One study reported total cholesterol:HDL ratio among patients with preexisting CHD.[89] Combination therapy reduced total cholesterol: HDL by 9 percent more than monotherapy.

***Low* potency statin combination therapy versus *mid* potency statin monotherapy**

No study reported total cholesterol: HDL ratio among patients with preexisting CHD.

Atherosclerosis

No study reported on atherosclerosis measures among patients with preexisting CHD.

Adherence

***Low* potency statin combination therapy versus *high* potency statin monotherapy**

No study reported on adherence among patients with preexisting CHD.

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**

Two studies reported on adherence among patients with preexisting CHD.[101,104] One study [104] showed similar adherence between groups, with adherence reported at >99 percent in both groups, although the authors did not provide detail on how they assessed adherence. The other study [101] assessed adherence by tablet count and showed a slight advantage to combination therapy (difference 1.5%).

***Low* potency statin combination therapy versus *mid* potency statin monotherapy**

No study reported on adherence among patients with preexisting CHD.

Any Adverse Event

***Low* potency statin combination therapy versus *high* potency statin monotherapy**

No study reported on occurrence of any adverse events among patients with preexisting CHD.

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**

Three studies reported on the occurrence of any adverse events among patients with preexisting CHD.[89,101,127] In one comparison, there was no difference between the two groups.[127] In two comparisons, more monotherapy group patients experienced this outcome (difference 3.9% to 7.5%).[89,101]

***Low* potency statin combination therapy versus *mid* potency statin monotherapy**

No study reported on occurrence of any adverse events among patients with preexisting CHD.

Withdrawal due to Adverse Events

***Low* potency statin combination therapy versus *high* potency statin monotherapy**

No study reported on withdrawals due to adverse events among patients with preexisting CHD.

Mid potency statin combination therapy versus high potency statin monotherapy

Five studies reported on withdrawals due to adverse events among patients with preexisting CHD.[89 101,106,127,128] In all comparisons, more monotherapy patients experienced this outcome (difference 1.4% to 17.9%).

Low potency statin combination therapy versus mid potency statin monotherapy

No study reported on withdrawals due to adverse events among patients with preexisting CHD.

Elevated Liver Transaminases

Low potency statin combination therapy versus high potency statin monotherapy

No study reported on elevated liver transaminases among patients with preexisting CHD.

Mid potency statin combination therapy versus high potency statin monotherapy

Six studies reported elevated liver transaminases (AST and/or ALT > 3 times ULN) among patients with preexisting CHD.[89,101,104,107,127,128] In four comparisons, there was no difference in this outcome. In one comparison, more combination therapy patients experienced LFT elevation (difference 0.5%) [89]; in another comparison more monotherapy patients experienced this adverse event (difference 2.6%) [104]

Low potency statin combination therapy versus mid potency statin monotherapy

No study reported on elevated liver transaminases among patients with preexisting CHD.

Musculoskeletal Adverse Events

Low potency statin combination therapy versus high potency statin monotherapy

No study reported on elevation in CPK or cases of myalgia among patients with preexisting CHD.

Mid potency statin combination therapy versus high potency statin monotherapy

Four studies reported on elevations in CPK > 10 times ULN among patients with preexisting CHD.[89,101,104,127] No participant experienced this event in any trial. One study reported on occurrence of myalgia among patients with preexisting CHD.[107] There were no reported cases of myalgia in either group.

Low potency statin combination therapy versus mid potency statin monotherapy

No study reported on elevation in CPK or cases of myalgia among patients with preexisting CHD.

Cancer

No study reported on cancer among patients with preexisting CHD.

New Onset Diabetes Mellitus

No study reported on cases of new onset diabetes mellitus among patients with preexisting CHD.

Acute Kidney Injury

No study reported on cases of acute kidney injury among patients with preexisting CHD.

Patients with Diabetes Mellitus

One study compared low potency statin therapy in combination with ezetimibe to high potency statin monotherapy in patients with DM.[84] Three studies compared mid potency statin in combination with ezetimibe to high potency statin monotherapy in patients with DM.[91-93,109,132] One study compared low potency statin in combination with ezetimibe to mid potency statin monotherapy in patients with DM.[129]

Mortality

Low potency statin combination therapy versus high potency statin monotherapy
No study reported on mortality among patients with DM.

Mid potency statin combination therapy versus high potency statin monotherapy
Two studies reported mortality among patients with DM.[91,93,109,132] Events were low. Two arms favored combination therapy, with 0.4 percent deaths in the monotherapy arm compared with 0 deaths in the combination arm and 0.5 percent deaths in the monotherapy arm compared with 0 deaths in the combination arm. P-value was not reported in one study [91] and was reported as non-significant in the other. [93,109,132] We graded the strength of evidence as insufficient (Table 18).

Low potency statin combination therapy versus mid potency statin monotherapy
No study reported on mortality among patients with DM.

Acute Coronary Events

No study reported on acute coronary events among patients with DM.

Cerebrovascular Disease

No study reported on cerebrovascular events among patients with DM.

Revascularization Procedures

No study reported on revascularization procedures among patients with DM.

Serious Adverse Events

Low potency statin combination therapy versus high potency statin monotherapy
No study reported on serious adverse events among patients with DM.

Mid potency statin combination therapy versus high potency statin monotherapy
Four studies (five arms) reported serious adverse events among patients with DM.[91,92,101,105] In four comparisons, there were more SAEs in the combo therapy group (difference 0.02% to 3.9%). In one comparison, there were more SAEs in the monotherapy group (difference 1.8%). We graded the strength of evidence as insufficient (Table 18).

Low potency statin combination therapy versus mid potency statin monotherapy
No study reported on serious adverse events among patients with DM.

LDL-c

Low potency statin combination therapy versus high potency statin monotherapy

One study reported LDL-c outcomes among patients with DM.[84] Monotherapy therapy lowered LDL-c 2 percent more than combination therapy. No studies reported LDL-c goal attainment. We graded the strength of evidence as insufficient (Table 17).

Mid potency statin combination therapy versus high potency statin monotherapy

Seven studies reported LDL-c outcomes among patients with DM.[91-93 ,101 ,109 ,132 105 89 ,103 ,110] In all studies, combination therapy lowered LDL more than monotherapy (difference 2.7% to 20.5%). We graded the strength of evidence as moderate. Two studies had multiple arms comparing mid potency statin combination therapy with different doses of high potency statin monotherapy.[93 109 105 ,132] Only the highest dose of statin monotherapy is shown in the Figure 15. Of the other comparison arms, two out of two favored combination therapy (difference 7.6% to 9%).

Three studies reported LDL-c goal attainment (LDL-c <100 mg/dL) among patients with DM.[91-93 ,109 ,132] Two studies reported that 2 percent to 37 percent more patients attained this LDL-c goal when taking combination therapy as compared to monotherapy;[92 ,93] however, the other study reported that 20 percent more patients in the monotherapy arm achieve this LDL-c goal as compared to combination therapy.[91] Another study reported on patients attaining an LDL-c <70 mg/dL among patients with DM.[101] This trial found that 18 percent more patients in the combination arm attained this LDL-c goal as compared to monotherapy.

Another reported LDL-c outcome in the subgroup of Black participants. This study only enrolled participants with DM. The LS mean percent change comparing combination therapy – monotherapy was -15 percent, again favoring combination therapy for LDL-c reduction. [92] One study reported LDL-c outcome in the subgroup of Hispanic participants. This study only enrolled participants with DM. The LS mean percent change comparing combination therapy – monotherapy was -26 percent, favoring combination therapy for LDL-c reduction. [92]

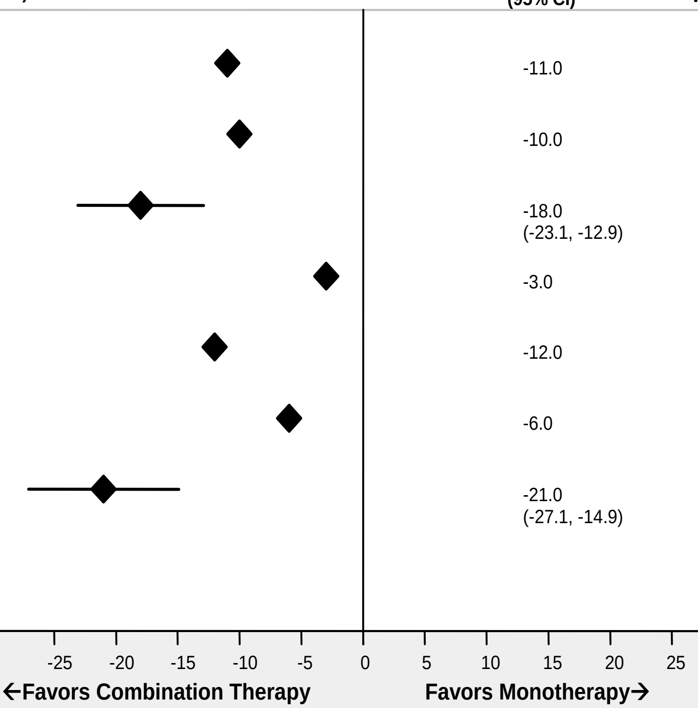
Meta-analysis is not reported due to high heterogeneity (I^2=100.0%).

Low potency statin combination therapy versus mid potency statin monotherapy

One study reported LDL-c outcomes among patients with DM.[129] Combination therapy lowered LDL-c 10 percent more than monotherapy. No studies reported LDL-c goal attainment. We graded the strength of evidence as insufficient (Table 19).

Figure 15: Mean difference in percent LDL-c change from baseline to time point comparing mid potency combination therapy with ezetimibe to high potency monotherapy among patients with DM

Author, Year	Statin Monotherapy	Combination therapy	Monotherapy Baseline LDL-c (mg/dL)	Combination Baseline LDL-c (mg/dL)	Between Group Difference (95% CI)	Timepoint weeks	N
Bardini, 2010	SMV 40mg	Ezetimibe10mg +SMV20mg	124	128	-11.0	6	NR
Barrios, 2005	ATV 20mg	Ezetimibe10mg +SMV20mg	NR	NR	-10.0	6	NR
Constance, 2007	ATV 20mg	Ezetimibe10mg +SMV20mg	93	89	-18.0 (-23.1, -12.9)	6	423
Goldberg 2006, Tomassini 2009,Guyton 2007	ATV 40mg	Ezetimibe10mg +SMV20mg	146	145	-3.0	6	479
Foody, 2010 (Subgroup)	ATV 20mg	Ezetimibe10mg +SMV20mg	NR	NR	-12.0	12	NR
Zieve 2010, Ben-Yehuda 2011 (Subgroup)	ATV 40mg	Ezetimibe10mg +ATV10mg	NR	NR	-6.0	12	216
Gaudiani, 2005	SMV 40mg	Ezetimibe10mg +SMV20mg	92	94	-21.0 (-27.1, -14.9)	24	210



ATV = atorvastatin; RSV= rosuvastatin; SMV= simvastatin
For diamonds without confidence intervals, SE/SD could not be calculated

HDL-c

Low potency statin combination therapy versus high potency statin monotherapy

One study reported HDL-c among patients with DM.[84] Combination therapy resulted in no change in HDL-c; however, monotherapy lowered HDL-c by 6 percent. We graded the strength of evidence as insufficient (Table 17).

Mid potency statin combination therapy versus high potency statin monotherapy

Six studies reported HDL-c among patients with DM (8 comparisons).[91-93,103,105,109,110,132] [101] In three studies, combination therapy increased HDL more than monotherapy (difference 1.8% to 5.7%).[92,103,105,110] Three studies were neutral (difference 0.1% to 0.74%)[92] Two studies had multiple arms comparing mid potency statin combination therapy with different doses of high potency statin monotherapy.[91 105] Only the highest dose of statin monotherapy is shown in the Figure 16. Of the other comparison arms, two out of two favored combination therapy (difference 3.8% to 4.5%).

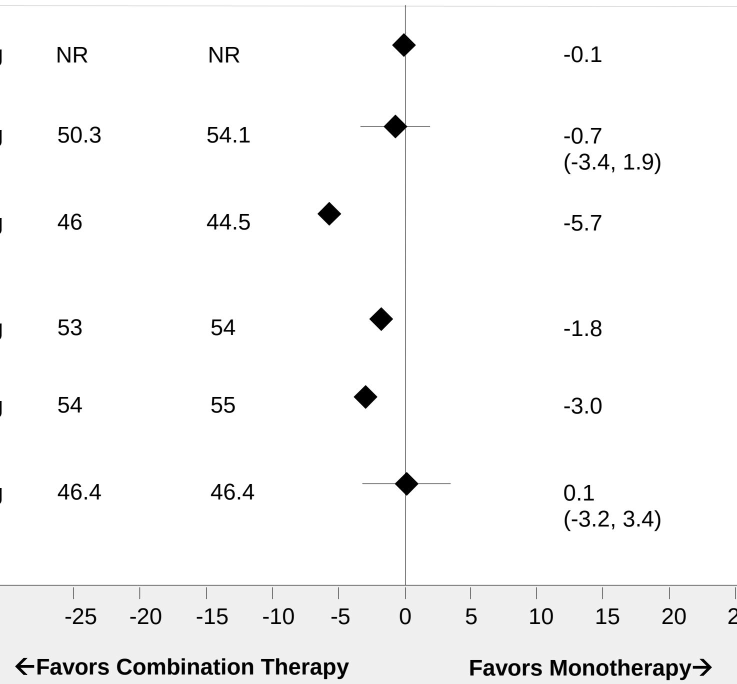
We graded the strength of evidence as moderate (Table 18). Meta-analysis was not reported due to high heterogeneity (I^2=100.0%).

Low potency statin combination therapy versus mid potency statin monotherapy

One study reported HDL-c among patients with DM.[129] Combination therapy increased HDL-c by 1 percent more than monotherapy. We graded the strength of evidence as insufficient (Table 19).

Figure 16: Mean difference in percent HDL change from baseline to time point comparing mid potency combination therapy with ezetimibe to high potency monotherapy in patients with DM

Author, Year	Statin Monotherapy	Combination Therapy	Monotherapy Baseline HDL-c (mg/dL)	Combination Baseline HDL-c (mg/dL)	Between Group Difference (95% CI)	Timepoint weeks	N
Bardini, 2010	SMV 40mg	Ezetimibe 10mg + SMV 20mg	NR	NR	-0.1	6	87
Constance, 2007	ATV 20mg	Ezetimibe 10mg + SMV 20mg	50.3	54.1	-0.7 (-3.4, 1.9)	6	437
Goldberg, 2006 Tomassini, 2009 Guyton, 2008	ATV 40mg	Ezetimibe 10mg + SMV 20mg	46	44.5	-5.7	6	479
Foody, 2010	ATV 40mg	Ezetimibe 10mg + SMV 20mg	53	54	-1.8	12	498
Zieve, 2010 Ben-Yehuda, 2011	ATV 40mg	Ezetimibe 10mg + ATV 10mg	54	55	-3.0	12	1030
Gaudiani, 2005	SMV 40mg	Ezetimibe 10mg + SMV 20mg	46.4	46.4	0.1 (-3.2, 3.4)	24	210



ATV atrovastatin; SMV simvastatin; NR not reported
For diamonds without confidence intervals, SE/SD could not be calculated

Total Cholesterol:HDL-c

***Low* potency statin combination therapy versus *high* potency statin monotherapy**

No study reported on total cholesterol: HDL ratio among patients with DM.

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**

Two studies reported total cholesterol:HDL ratio among patients with DM.[91,92] Combination therapy lowered total cholesterol: HDL by 9.41 percent to 13.5 percent more than monotherapy.

***Low* potency statin combination therapy versus *mid* potency statin monotherapy**

No study reported on total cholesterol: HDL ratio among patients with DM.

Non-HDL-c

***Low* potency statin combination therapy versus *high* potency statin monotherapy**

No study reported on non-HDL-c among patients with DM.

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**

Three studies reported on non-HDL-c among patients with DM (4 arms).[91-93,109,132] Three arms favored combination therapy for lowering non-HDL [92,93], lowering non-HDL by 20 to 47.9 percent (difference 1.7% to 18.3%). One arm favored monotherapy [91], and in that study non-HDL was raised in both groups (raised by 7.43% in the atorvastatin 20 arm and raised by 20.91% in the simvastatin 20/ezetimibe10 arm).

***Low* potency statin combination therapy versus *mid* potency statin monotherapy**

No study reported on non-HDL-c among patients with DM.

Triglycerides

***Low* potency statin combination therapy versus *high* potency statin monotherapy**

No study reported on triglycerides among patients with DM.

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**

Four studies reported on triglycerides among patients with DM (four arms).[91-93,109,132 101] Two arms [93 109 91,132] favored monotherapy for triglyceride reduction (difference 2.7% to 4.26%). Two arms favored combination therapy [92,101] for triglyceride reduction (difference 4.5% to 6.7%).

***Low* potency statin combination therapy versus *mid* potency statin monotherapy**

No study reported on triglycerides among patients with DM.

Atherosclerosis

No study reported on measures of atherosclerosis among patients with DM.

Adherence

***Low* potency statin combination therapy versus *high* potency statin monotherapy**

No study reported on adherence among patients with DM.

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**

One study reported adherence [91], and showed similar high (98% adherence) adherence between both arms, although the authors did not provide details on how adherence was assessed.

***Low* potency statin combination therapy versus *mid* potency statin monotherapy**

No study reported on adherence among patients with DM.

Musculoskeletal Adverse Events

***Low* potency statin combination therapy versus *high* potency statin monotherapy**

No study reported on elevations in CPK or cases of myalgia among patients with DM.

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**

Two studies reported on cases of myalgia among patients with DM.[91,92] Events were low and one study favored monotherapy (0.5% in combination therapy patients, 0% in monotherapy patients). [91] In the other study no events were reported in either arm. [92] One study reported on elevations of CPK > 10 times ULN.[92] Monotherapy was favored.

***Low* potency statin combination therapy versus *mid* potency statin monotherapy**

No study reported on elevations in CPK or cases of myalgia among patients with DM.

Elevated Liver Transaminases

No study reported on elevations in liver transaminases among patients with DM.

Withdrawal due to Adverse Events

***Low* potency statin combination therapy versus *high* potency statin monotherapy**

No study reported on withdrawals due to adverse events among patients with DM.

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**

Four studies reported withdrawals due to adverse events among patients with DM.[91,92,101,105] Outcomes were low. In two comparisons, there were more withdrawals due to AE in the monotherapy arm than in the combination therapy arm (difference 1.5% to 2.9%)[92,101] In three comparisons, there were more withdrawals in the combination therapy group (difference 0.5% to 2.3%).[92,105]

***Low* potency statin combination therapy versus *mid* potency statin monotherapy**

No study reported on withdrawals due to adverse events among patients with DM.

Any Adverse Event

***Low* potency statin combination therapy versus *high* potency statin monotherapy**

No study reported on occurrence of any adverse events among patients with DM.

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**

Four studies (five comparisons) reported on occurrence of any adverse events among patients with DM.[91,92,101,105] In four comparisons, there were more AEs in the combination therapy group (difference 1.5% to 8.3%). In one comparison, there were more AEs in the monotherapy group (difference 7.5%).

Low potency statin combination therapy versus mid potency statin monotherapy
No study reported on occurrence of any adverse events among patients with DM.

Cancer

No study reported on cancer among patients with DM.

Acute Kidney Injury

No study reported on acute kidney injury among patients with DM.

Elderly Patients (> 75 years old)

Two studies reported outcomes for elderly participants.[103,105,110] These trials compared mid potency statin in combination with ezetimibe to high potency statin monotherapy. With respect to clinical outcomes, these studies only reported on mortality and serious adverse events. With respect to surrogate outcomes, they reported on LDL-c, HDL-c, and total cholesterol:HDL ratio. With respect to short-term harms, these trials reported only on

Mortality

Mid potency statin combination therapy versus high potency statin monotherapy

No deaths occurred in the one study that examined this outcome among elderly patients.[103,110] We graded the strength of evidence as insufficient

Serious Adverse Events

Mid potency statin combination therapy versus high potency statin monotherapy

One study reported on serious adverse events among elderly patients.[103,110] This study reported that 3 percent of elderly patients in the combination arm had a serious adverse event, while no elderly patients in the monotherapy group experienced a serious adverse event. We graded the strength of evidence as insufficient.

LDL-c

Mid potency statin combination therapy versus high potency statin monotherapy

Two studies reported on LDL-c outcomes among elderly patients.[103,105,110]

The LS mean percent change in LDL-c was 14 percent among the elderly participants in the monotherapy arm vs. 28.4 percent among the elderly participants in the combination therapy arm at 6 weeks ($p<0.05$); the LS mean percent change in LDL-c was -20.2 percent in the monotherapy group and -20.6 percent in the combination therapy group at 12 weeks ($p>0.05$).

Another study reported LDL-c change in the elderly subgroup [105] and favored combination therapy for LDL-c change (47.5% decrease in the monotherapy arm compared with 58% decrease in the combination therapy arm).

One study [103,110] examined LDL-c goal attainment in elderly patients, and reported that 45 percent of elderly patients in the combination therapy arm and 56 percent of patients in the monotherapy arm attained LDL-c goals at 12 weeks. We graded the strength of evidence as insufficient.

HDL-c

Mid potency statin combination therapy versus high potency statin monotherapy

One study examined HDL-c among elderly patients.[103,110] This study favored combination therapy at 6 weeks (0.6% HDL-c increase in monotherapy group at 6 weeks, 3.6% HDL-c increase in monotherapy group at 6 weeks) and at 12 weeks (1.4% HDL-c decrease in monotherapy group at 12 weeks, 2.4% HDL-c increase in combination therapy group at 12 weeks). We graded the strength of evidence as insufficient.

Total Cholesterol:HDL

Mid potency statin combination therapy versus high potency statin monotherapy

One study examined total cholesterol: HDL-c change in elderly patients.[103,110] Combination therapy was favored, with a 7.8 percent decrease in total cholesterol:HDL in monotherapy arm participants at 6 weeks, a 19 percent decrease in combination therapy arm participants at 6 weeks; a 10.8 percent decrease in monotherapy participants at 12 weeks and a 14.2 percent decrease in combination therapy patients at 12 weeks.

Any Adverse Event

Mid potency statin combination therapy versus high potency statin monotherapy

One study [103,110] reported adverse events in elderly patients. 31 percent of elderly participants in the monotherapy arm had an AE by 12 weeks, while 30 percent in the combination arm had an AE by 12 weeks.

Withdrawal AE

Mid potency statin combination therapy versus high potency statin monotherapy

One study [103,110] reported withdrawal due to adverse events in elderly patients. 2 percent of elderly participants in the monotherapy arm withdrew due to AE by 12 weeks, while 6 percent in the combination arm withdrew due to AE by 12 weeks.

Elevated Liver Transaminases

Mid potency statin combination therapy versus high potency statin monotherapy

One study examined elevated liver transaminases in elderly patients, which was 0 percent in both groups at 12 weeks.[103,110]

Musculoskeletal Adverse Events

Mid potency statin combination therapy versus high potency statin monotherapy

One study [103,110] examined elevated CPK > 10x ULN in elderly patients, which was 0 percent in both groups at 12 weeks.

Female Patients

Two studies reported outcomes for female participants.[103,105,110] Both trials compared a mid potency statin in combination with ezetimibe to high potency statin monotherapy. These trials only reported on LDL-c outcomes.

LDL-c

Mid potency statin combination therapy versus high potency statin monotherapy

Two studies reported LDL-c outcome among female participants.[103,105,110]Combination therapy lowered LDL-c more than monotherapy (difference 8 percent to 13.5 percent).

We graded the strength of evidence as insufficient.

Asian Patients

One study reported outcomes for Asian participants.[105] This trial compared a mid potency statin in combination with ezetimibe to high potency statin monotherapy. This trial only reported on LDL-c outcomes.

LDL-c

Mid potency statin combination therapy versus high potency statin monotherapy

The one study that reported on LDL-c among Asian participants reported that monotherapy decreased LDL-c by 8 percent more than combination therapy. We graded the strength of evidence as insufficient.

Black Patients

One study reported outcomes for black participants.[105] This trial compared a mid potency statin in combination with ezetimibe to high potency statin monotherapy. This trial only reported on LDL-c outcomes.

LDL-c

Mid potency statin combination therapy versus high potency statin monotherapy

The one study that reported on LDL-c among black participants reported that combination therapy decreased LDL-c by 15 percent more than monotherapy. We graded the strength of evidence as insufficient.

Table 11: Low potency statin in combination with ezetimibe as compared to high potency statin monotherapy in <u>general populations</u>: strength of evidence

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long Term Benefits and Serious Adverse Events								
Mortality	2 (199)	Low	NA	Consistent [favors mono]	Imprecise	Not detected None	Findings favor monotherapy: In both trials, there was one death in a combination therapy arm and no deaths in monotherapy arms.	Insufficient
Acute Coronary Events	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Serious Adverse Events	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Surrogate Clinical Outcomes								
LDL-c	12 (1571)	Moderate	Indirect [LDL not directly measured in all trials]	Inconsistent [six favored combination, three neutral, three monotherapy]	Imprecise	Not detected None	Six comparisons favored combination therapy for lowering LDL-c as compared to monotherapy (difference 2 percent to 12 percent).	Low
HDL-c	10 (1352)	Moderate	Direct [HDL directly measured]	Inconsistent [three favored combination, six neutral, one monotherapy]]	Imprecise	Not detected None	Three comparisons favored combination therapy for raising HDL-c as compared to monotherapy (difference5.14 percent to 6.3 percent).	Low

LDL= low density lipoprotein; HDL=high density lipoprotein; NA =not applicable

Table 12: Mid potency statin in combination with ezetimibe as compared to high potency statin monotherapy in <u>general populations</u>: strength of evidence

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long Term Benefits and Serious Adverse Events								
Mortality	7 (4300)	Low	Direct	Inconsistent	Imprecise [does not meet OIS of 4864]	Not detected None	Very few events; similar mortality in combination therapy and monotherapy arms.	Insufficient
Acute Coronary Events	1 (621)	Low	Direct	NA	Imprecise	Not detected None	Only one event occurring in a combination arm.	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Serious Adverse Events	3 (2397)	Low	Direct	Consistent [1 showed no diff; 2 favored mono]	Precise [meets OIS of 1490]	Not detected None	Two studies favored monotherapy.	High
Surrogate Clinical Outcomes								
LDL-c	12 (5991)	Low	Indirect [LDL calculated not directly measured in most trials]	Consistent [Eight studies favored combination therapy, two were neutral, two favored monotherapy]	Imprecise	Not detected None	Eight comparisons favored combination therapy for lowering LDL-c as compared to monotherapy (difference 3 percent to 18 percent)	Moderate
HDL-c	11 (5991)	Low	Direct [HDL directly measured]	Inconsistent [Six studies favored combination therapy, five neutral]	Imprecise	Not detected None	Six comparisons favored combination therapy for raising HDL-c as compared to monotherapy (difference 1.8 percent to 6 percent)	Low

LDL= low density lipoprotein; HDL=high density lipoprotein; NA =not applicable

Table 13: Low potency statin in combination with ezetimibe as compared to mid potency statin monotherapy in general populations: strength of evidence

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long Term Benefits and Serious Adverse Events								
Mortality	2 (128)	Low	NA	NA [no deaths either arm]	Imprecise	Not detected None	No deaths in included arms.	Insufficient
Acute Coronary Events	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Serious Adverse Events	1 (504)	High	Direct	NA	Imprecise [OIS 640]	NA	There were more SAEs in the combination therapy arm than the monotherapy arm.	Insufficient
Surrogate Clinical Outcomes								
LDL-c	7 (1195)	Low]	Indirect [LDL calculated not directly measured in both trials]	Consistent [All trials favor combination therapy]	Imprecise	Not detected None	All comparisons favored combination therapy for lowering LDL-c as compared to monotherapy (difference 3 percent to 11.3 percent).	Moderate
HDL-c	6 (1195)	Low	Direct [HDL calculated directly]	Inconsistent [Three trials favored combination therapy, three were neutral]	Imprecise	Not detected None	Three studies favored combination therapy for raising HDL-c as compared to monotherapy (difference 3 percent to 4 percent)	Low

LDL= low density lipoprotein; HDL=high density lipoprotein; NA =not applicable

Table 14: Low potency statin in combination with ezetimibe as compared to high potency statin monotherapy among patients with CHD: strength of evidence

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long Term Benefits and Serious Adverse Events								
Mortality	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Acute Coronary Events	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Serious Adverse Events	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Surrogate Clinical Outcomes								
LDL-c	1 (84)	High	Indirect [LDL calculated not directly measured in both trials]	NA	Imprecise	Not detected None	One trial favored combination therapy, lowering LDL by 5 % more than monotherapy	Insufficient
HDL-c	1 (84)	High	Direct [HDL directly measured]	NA	Imprecise	Not detected None	In one trial, Combination therapy raised HDL-c 9 percent more than monotherapy.	Insufficient

LDL= low density lipoprotein; HDL=high density lipoprotein; NA =not applicable; CHD coronary heart disease

Table 15: Mid potency statin in combination with ezetimibe as compared to high potency statin monotherapy among patients with CHD: strength of evidence

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long Term Benefits and Serious Adverse Events								
Mortality	3 (914)	Low	Direct	NA [No deaths either arm]	Imprecise	Not detected None	No mortality in any arm of any trial.	Insufficient
Acute Coronary Events	1 (49)	High	Direct	NA	Imprecise	Not detected None	Fatal MI in the combination arm.	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Serious Adverse Events	3 (634)	Low	Direct	Inconsistent [2 favored mono, 1 favored combo]	Imprecise [does not meet OIS of 1864]	Not detected None	Two studies favored monotherapy; one favored combination therapy.	Insufficient
Surrogate Clinical Outcomes								
LDL-c	10 (1050)	Low	Indirect [LDL calculated not directly measured in all trials]	Consistent [most but not all favored combo]	Imprecise	Not detected None	In nine comparisons, combination therapy lowered LDL more than monotherapy (difference 5 percent to 15 percent)	Moderate
HDL-c	9 (683)	Low	Direct [HDL directly measured]	Inconsistent [Mixed results – most neutral]	Imprecise	Not detected None	Most studies were neutral (difference 0.1 percent to 5.6%, NS)	Low

LDL= low density lipoprotein; HDL=high density lipoprotein; NA =not applicable; CHD coronary heart disease

Table 16: Low potency statin in combination with ezetimibe as compared to mid potency statin monotherapy among patients with CHD: strength of evidence

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long Term Benefits and Serious Adverse Events								
Mortality	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Acute Coronary Events	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Serious Adverse Events	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Surrogate Clinical Outcomes								
LDL-c	2 (138)	High	Indirect [LDL calculated not directly measured in both trials]	Consistent [Both trials favor combination]	Imprecise	Not detected None	Both trials favored combination therapy for LDL-c reduction (difference 1.6 to 8.3 percent)..	Insufficient
HDL-c	2 (138)	High	Direct [HDL directly measured]	Inconsistent [one mono, one combo]	Imprecise	Not detected None	One study favored combination therapy to increase HDL (difference .29 percent) while one study favored monotherapy to increase HDL (difference 7.71 percent).	Insufficient

LDL= low density lipoprotein; HDL=high density lipoprotein; NA =not applicable; CHD coronary heart disease

Table 17: Low potency statin in combination with ezetimibe as compared to high potency statin monotherapy among patients with DM: strength of evidence

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long Term Benefits and Serious Adverse Events								
Mortality	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Acute Coronary Events	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Serious Adverse Events	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Surrogate Clinical Outcomes								
LDL-c	1 (21)	Low	Indirect [LDL calculated]	NA	Imprecise	Not detected None	Monotherapy therapy lowered LDL-c 2 percent more than combination therapy.	Insufficient
HDL-c	1 (21)	Low	Direct [HDL calculated directly]	NA	Imprecise	Not detected None	Combination therapy resulted in no change in HDL-c; however, monotherapy lowered HDL-c by 6 percent.	Insufficient

LDL= low density lipoprotein; HDL=high density lipoprotein; NA =not applicable; DM= diabetes mellitus

Table 18: Mid potency statin in combination with ezetimibe as compared to high potency statin monotherapy among patients with DM: strength of evidence

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long Term Benefits and Serious Adverse Events								
Mortality	2 (1176)	Low	Direct	Consistent [favored combo]	Imprecise	Not detected None	Events low overall but more frequent in monotherapy arm.	Insufficient
Acute Coronary Events	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Serious Adverse Events	3 (746)	Low	Direct	Inconsistent [one mono, 1 combo]	Imprecise [does not meet OIS of 1208]	Not detected None	One study favored monotherapy while one favored combination therapy.	Insufficient
Surrogate Clinical Outcomes								
LDL-c	7 (1581)	Low [< 1/2 trials low quality]	Indirect [LDL not directly measured in all trials]	Consistent [All trials favor high potency statin monotherapy]	Precise	Not detected None	In all studies, combination therapy lowered LDL more than monotherapy (difference 2.7 percent to 20.5 percent).	Moderate
HDL-c	5 (1700)	Low]	Direct [HDL calculated directly]	Consistent [favor mono therapy or neutral]	Imprecise	Not detected None	In three studies, combination therapy increased HDL more than monotherapy (difference 1.8 percent to 5.7 percent)	Moderate

LDL= low density lipoprotein; HDL=high density lipoprotein; NA =not applicable; DM= diabetes mellitus

Table 19: Low potency statin in combination with ezetimibe as compared to mid potency statin monotherapy among patients with DM: strength of evidence

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long Term Benefits and Serious Adverse Events								
Mortality	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Acute Coronary Events	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Serious Adverse Events	None	NA	NA	NA	NA	NA	No eligible studies	Insufficient
Surrogate Clinical Outcomes								
LDL-c	1 (24)	High	NR [not recorded if LDL was measured or calculated]	NA	Imprecise	Not detected None	Combination therapy lowered LDL-c 10% more than monotherapy.	Insufficient
HDL-c	1 (24)	Low	Direct [HDL calculated directly]	NA	Imprecise	Not detected None	Combination therapy increased HDL-c by 1% more than monotherapy.	Insufficient

LDL= low density lipoprotein; HDL=high density lipoprotein; NA =not applicable; DM= diabetes mellitus

Combined Lipid-Modifying Therapy with Statin and Fibrate versus Intensification of Statin Monotherapy

Study Characteristics

We included 8 RCTs (3,099 participants in eligible arms) that compared fibrate plus statin to intensification of statin monotherapy.[74,111-117,131] All trials were parallel arm RCTS. Three studies were multicenter trials conducted in North America.[113,115,116] Four studies occurred in Europe, one was multicenter[131] and three were single center.[74,111,112,114] One study was a single center trial in Asia.[117] Only one trial did not include a dietary run in.[117] The treatment duration ranged from 8 to 52 weeks. Most trials included general populations of patients with hyperlipidemia.[74,111-116] One study included only patients with recent ACS requiring percutaneous inventions, which was one of our subgroups of interest.[117] Another study included only patients with type 2 diabetes with no known coronary artery disease, which was also one of our subgroups of interest.[131] Six trials compared high potency statin monotherapy to mid potency statin in combination therapy.[74,111-116] One trial also allowed comparisons of high potency statin monotherapy to low potency statin in combination with fibrate.[74] One trial allowed for comparison of high potency statin monotherapy to mid potency statin combination therapy with fibrate among patients with preexisting CHD.[117] One study compared mid potency statin monotherapy to low potency statin in combination therapy among patients with diabetes.[131] (Appendix E Evidence Tables)

Population Characteristics

The average participant was in their 50s with the mean age ranging from 50 to 58 years.[74,111-114,117,131] The proportion of female participants varied across trials, ranging from less than 20 percent to 68 percent. Smoking status, prior cardiovascular disease, revascularization events, and diabetes were not consistently reported across trials. Race was reported in five trials, and over 80 percent of participants were white.[113,115,116,131] (Appendix E Evidence Tables)

Interventions

Six trials compared mid potency statin in combination with fibrates to high potency statin monotherapy.[74,111-116] The type of statin varied across trials: three trials used rosuvastatin,[111-114] and three trials used simvastatin.[74,115,116] One study compared low potency statin in combination with fibrates to high potency statin monotherapy, and used pravastatin.[74] Another study compared mid potency statin in combination with fibrates to high potency statin among patients with preexisting CHD.[117] One study compared low potency statin in combination with fibrates to mid potency statin monotherapy among diabetics,[131] and used simvastatin. The trials used fenofibric acid, fenofibrate, gemfibrozil, or ciprofibrate in the combination arms.

Outcomes

Key Points

- **Long-Term Benefits**

- There is insufficient evidence to compare the long-term benefits of combined lipid-modifying therapy with fibrate and statin to intensification of statin monotherapy at any statin potency.

- **Serious Adverse Events**
  - There is insufficient evidence to compare the serious adverse events of combined lipid-modifying therapy with fibrate and statin to intensification of statin monotherapy at any statin potency.
- **Surrogate Outcomes**
  - High potency statin monotherpy is more effective than a mid potency statin in combination with fibrate for lowering LDL-c (SOE: moderate). There is insufficient evidence within other potency comparisons.
  - A mid potency statin in combination with fibrate is more effective than high potency statin monotherapy for raising HDL-c (SOE: moderate). There is insufficient evidence within other potency comparisons.
- **Short-Term Side Effects**
  - The evidence suggests that there is little to no difference with respect to elevations in liver transaminases when comparing mid potency statin combination with fibrate to high potency statin monotherapy. There is insufficient evidence within other potency comparisons.
  - The evidence suggests that there is little to no difference with respect to elevations in creatinine phosphokinase when comparing mid potency statin combination with fibrate to high potency statin monotherapy. There is insufficient evidence within other potency comparisons.
  - The evidence favors high potency statin monotherapy for minimizing withdrawals due to adverse events as compared to mid potency statin in combination with fibrate. There is insufficient evidence within other potency comparisons.
- **Adherence**
  - There is insufficient evidence to compare medication adherence between combined lipid-modifying therapy with fibrate and statin to intensification of statin monotherapy at any statin potency.
- **Subgroups**
  - There is insufficient evidence to compare the long-term benefits of combined lipid-modifying therapy with fibrate and statin to intensification of statin monotherapy among any subgroup at any statin potency.
  - There is insufficient evidence to compare the harms of combined lipid-modifying therapy with fibrate and statin to intensification of statin monotherapy among any subgroup at any statin potency.

Long-term benefits and serious adverse events (KQ1)

Few studies reported on the comparative effectiveness of fibrate plus statin on long-term benefits as compared to intensification of statin monotherapy among adults. We graded the strength of evidence for mortality, acute coronary events, revascularization procedures, and serious adverse events as insufficient. We identified no studies that compared high potency statin monotherapy to low potency statin combination therapy reported data for key question 1.

Mortality

***Mid** potency statin combination therapy versus **high** potency statin monotherapy*

One RCT reported mortality. [116] This trial reported no deaths in either arm during the 12-week followup.

Acute Coronary Events

No studies reported on acute coronary events.

Cerebrovascular Disease

No studies reported on cerebrovascular events.

Revascularization Procedures

No studies reported on revascularization procedures

Serious Adverse Events

***Mid** potency statin combination therapy versus **high** potency statin monotherapy*

One RCT reported on serious adverse evetns.[116] No severe adverse events occurred in high potency statin monotherapy arm, while 1 event (0.8%) and 4 events (3.4%) occurred in the mid potency statin combination arms during 12 weeks of followup.

Surrogate outcomes, short-term side effects and adherence (KQ2)

All included RCTs evaluated surrogate outcomes including LDL -c and HDL-c. In a few RCTs, LDL-c goal attainment, total cholesterol:HDL ratio, medication adherence and adverse events including withdrawal, elevated liver transaminases elevated creatinine phosphokinase, rhabdomyolysis, myalgia, and new diagnosis of acute kidney injury were evaluated. We identified no eligible non-randomized extensions of RCTs or FDA reports.

LDL -c

***Low** potency statin combination therapy versus **high** potency statin monotherapy*

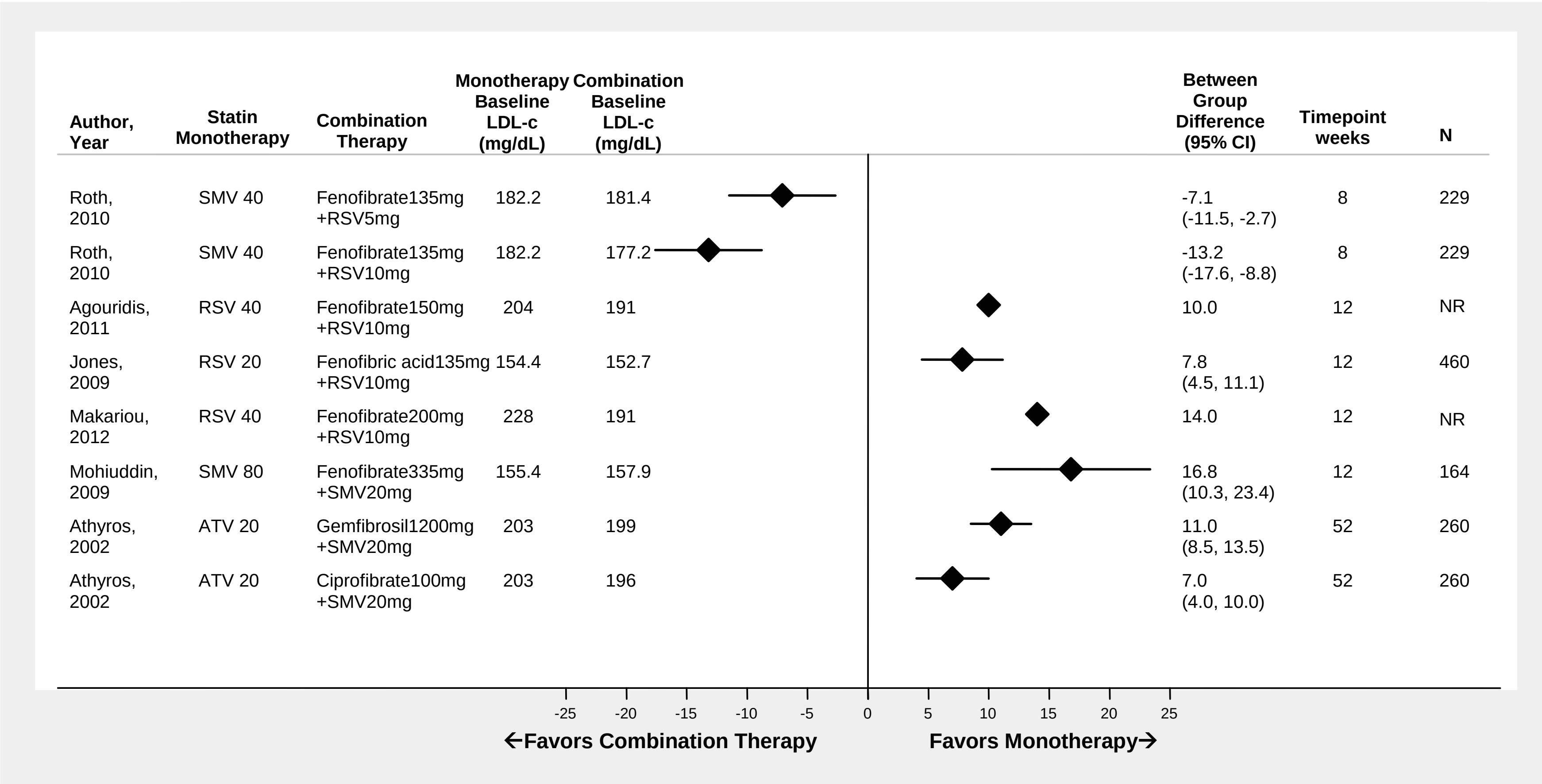
One trial reported mean percent change in LDL-c.[74] At 12 months, monotherapy lowered LDL-c 6 percent and 11 percent more than the two combination arms. This trial also reported LDL-c goal attainment, which similarly favored monotherapy (32 percent and 45 percent more patients in monotherapy arm). We graded the strength of evidence as insufficient es (Tables 20).

***Mid** potency statin combination therapy versus **high** potency statin monotherapy*

Overall, six trials reported mean precent change in LDL-c.[74,111-116] In five trials, monotherapy lowered LDL-c 5 percent to 17 percent more than combination therapy.[74,111-115] Duration of these trials ranged from 12 weeks (n=4) to 12 months (n=1). Two of these trials also reported the proportion of patients achieving LDL-c target.[74,111,112] In both trials, 17 percent to 29 percent more patients in the monotherapy arms achieved their LDL-c goals as compared to patients in the monotherapy arms. Only one trial favored combination therapy.[116] The two combination arms lowered LDL-c 7 percent and 13 percent more than the monotherapy arm. This trial also reported the proportion of patients achieving LDL-c target, which similarly favored combination therapy (difference 23% and 46%).

The results of almost all comparisons favored high potency statin monotherapy for lowering LDL-c (Figure 17). A single trial favored combination therapy,[116] which had higher baseline LDL-c level as compared to the other trials. This fact may contribute to the different results observed in this trial. We graded the strength of evidence as moderate (Table 19). While six trials reported on this comparison, only four of the trials reported on SE for the LDL-c difference in differences. We imputed SE for the additional two trials. Meta-analysis that included all six trials and sensitivity meta-analysis that only included the four trials with reported SE both demonstrated substantial heterogeneity (I^2 = 96% and 97%, respectively). Therefore we do not present these results.

Figure 17: Mean difference in percent LDL change from baseline to time point comparing mid potency combination therapy with fibrates to high potency statin monotherapy



ATV atorvastatin; RSV rosuvastatin; SMV simvastatin; NR not reported
For diamonds without confidence intervals, SE/SD could not be calculated

HDL-c

***Low* potency statin combination therapy versus *high* potency statin monotherapy**

One trial reported mean percent change in HDL-c.[74] At 12 months, combination therapy was more effective at increasing HDL-c than monotherapy (difference 9% and 11% favoring combination therapy arms). We graded the strength of evidence as insufficient (Table 20).

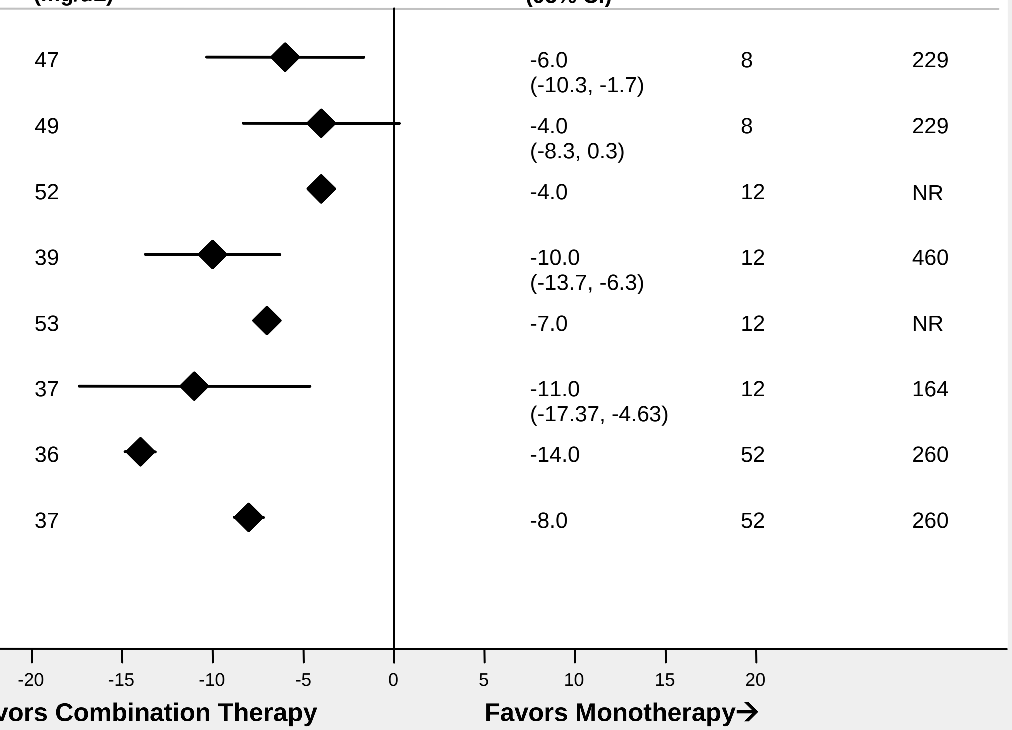
***Mid* potency statin combination therapy versus *high* potency statin monotherapy**

Six trials reported mean percent change in HDL-c.[74,111-116] In all trials, combination therapy raised HDL-c 4 percent to 14 percent more than monotherapy (Figure 18). Duration of trials ranged from 8 weeks to 12 months. We graded the strength of evidence as moderate. Only four trials provided sufficient information to calculate SE for the HDL-c difference in differences, which were also of similar duration (8 to 12 weeks). [74]

Only four of the trials reported on SE for the LDL-c difference in differences. We imputed SE for the additional two trials. Meta-analysis that included all six trials showed that combination therapy significantly raised HDL-c 6.9 percent more than monotherapy (95% CI 4.6 to 9.2; $p<0.001$; $I^2 = 35\%$). Sensitivity meta-analysis that only included the four trials with reported SE showed that combination therapy significantly raised HDL-c 7.5 percent more than monotherapy (95% CI 4.3 to 10.7; $p<0.001$; $I^2 = 49\%$).

Figure 18: Mean difference in percent HDL change from baseline to time point comparing mid potency combination therapy with fibrates to high potency statin monotherapy

Author, Year	Statin Monotherapy	Combination Therapy	Monotherapy Baseline HDL-c (mg/dL)	Combination Baseline HDL-c (mg/dL)	Between Group Difference (95% CI)	Timepoint weeks	N
Roth, 2010	SMV 40	Fenofibrate135mg +RSV5mg	49	47	-6.0 (-10.3, -1.7)	8	229
Roth, 2010	SMV 40	Fenofibrate135mg +RSV10mg	49	49	-4.0 (-8.3, 0.3)	8	229
Agouridis, 2011	RSV 40	Fenofibrate150mg +RSV10mg	50	52	-4.0	12	NR
Jones, 2009	RSV 20	Fenofibric acid135mg +RSV10mg	39	39	-10.0 (-13.7, -6.3)	12	460
Makariou, 2012	RSV 40	Fenofibrate200mg +RSV10mg	54	53	-7.0	12	NR
Mohiuddin, 2009	SMV 80	Fenofibrate335mg +SMV20mg	40	37	-11.0 (-17.37, -4.63)	12	164
Athyros, 2002	ATV 20	Gemfibrosil1200mg +SMV20mg	36	36	-14.0	52	260
Athyros, 2002	ATV 20	Ciprofibrate100mg +SMV20mg	36	37	-8.0	52	260



ATV atorvastatin; RSV rosuvastatin; SMV simvastatin; NR not reported
For diamonds without confidence intervals, SE/SD could not be calculated

Total Cholesterol:HDL Ratio

***Low* potency statin combination therapy versus *high* potency statin monotherapy**

One trial reported mean percent change in total cholesterol:HDL ratio.[74] The monotherapy arm decresed total cholesterol:HDL by 0 percent to 4 percent more than combination therapy. There was no statistically significant between group differences.

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**

One trial reported mean percent change in total cholesterol:HDL ratio.[74] Combination significantly lowered total cholesterol:HDL by two percent more than monotherapy at 12 months.[74]

Adherence

***Low* potency statin combination therapy versus *high* potency statin monotherapy**

No studies reported on adherence.

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**

One trial reported that compliance was 97 percent in both combination and monotherapy arms.[116]

Any Adverse Events

***Low* potency statin combination therapy versus *high* potency statin monotherapy**

No studies reported on occurrence of at least one adverse event.

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**

Two trials reported on the occurrence of at least one adverse event.[115,116] In one study, fewer particpants in the combination therapy arms experienced at least one adverse event (3% and 11% fewer favoring combination therapy. The other trial reported fewer participants experiencing at least one adverse event in the monotherapy arm (2% and 12% fewer).[115]

Withdrawal due to Adverse Events

***Low* potency statin combination therapy versus *high* potency statin monotherapy**

No studies reported on withdrawals due to an adverse event.

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**

Four trials reported on withdrawals due to adverse events.[111-113,115,116] Two trials reported more withdrawals due to adverse events in the combination therapy arms at 12 weeks.[111-113] In one of these trials, 13 participants withdrew in the monotherapy arm and 25 participants withdrew from the combination arm.[113] Another trial reported more withdrawals in the monotherapy arm as compared to the two combination arms.[116] The final trial reported that discontinuation of medication due to adverse events were similar in each arm.[115] Overall, the evidence may suggest that withdrawal due to adverse events was more common among participants in the combination therapy arms

Cancer

No studies reported on cancer.

Elevated Liver Transaminases

***Low* potency statin combination therapy versus *high* potency statin monotherapy**

One trial reported on elevated liver transaminases (AST and/or ALT greater than 3 times ULN).[74] At 12 months, no cases of elevated liver transaminases were found in the monotherapy arm, while 1 case found in a combination arm.[74]

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**

Four trials reported on elevated liver transaminases (AST and/or ALT greater than 3 times ULN).[74,111,112,115,116] Overall, few cases of elevated live transaminases occurred. Two trials had no cases in either arm.[111,112,116] One trial had one case in the monotherapy arm, while none were reported in the combination arm.[115] At 12 months, the final trial reported no cases of elevated liver transaminases in the monotherapy arm, while 3 cases were found in two combination therapy arms.[74] Overall, the evidence suggests that there is little to no difference between high potency statin monotherapy and mid potency statin combined with fibrate with respect to elevated liver transaminases.

Musculoskelatal Adverse Events

***Low* potency statin combination therapy versus *high* potency statin monotherapy**

One trial reported on elevations of CPK greater than 3 times the upper limit of normal.[74] At 12 months, there were no reported cases in the monotherapy arm and one case was identified in one of low potency statin in combination therapy arms.

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**

Four trials reported on elevations of CPK greater than 10 times the upper limit of normal.[113,115,116] At 12 weeks, there were no cases of elevations of CPK greater than 10 times the upper limit of normal in either arm.[116] At 12 weeks, one case was found in the monotherapy arm and none in the combination arm.[113] Another trial reported that at 12 weeks there were 2 cases in the combination arm and none in monotherapy arm.[115] The last trial reported that there were no cases in the monotherapy arm and 1 case in one of two combination therapy arms at 12 months.[74] Overall, the evidence suggests that there is little to no difference between high potency statin monotherapy and mid potency statin combined with fibrate with respect to elevated CPK.

Three trials reported on occurrences of myalgia.[111-113,115] At 12 weeks, there were no reported cases of myalgia in the monotherapy arm and 2 cases in the combination therapy arm.[111,112] At 12 weeks, 9 cases of myalgia were reported in the monotherapy arm and 10 cases in the combination arm.[113] Another trial reported that 5 percent of participants had myalgia in the both monotherapy arms and 4 percent of participants had mylagia in the combination arm.[115]

Finally, two studies reported that there were no cases of rhabdomyolysis identified in either arm during followup.[115,116]

New Onset Diabetes Mellitus

No studies reported on new onset diabetes.

Acute Kidney Injury

***Low* potency statin combination therapy versus *high* potency statin monotherapy**
No studies reported on acute kidney injury for this comparison.

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**
Two trials reported on investigator defined acute kidney injury.[113,116] At 12 weeks, no cases were identified in the monotherapy arm, while 1 and 3 cases occurred in the combination therapy arms.[116] At 12 weeks, 1 case in each monotherapy arm and 7 cases in the combination arm.[113]

Subgroups of patients (KQ3)

We identified two trials that occurred exclusively among two of our a priori defined subgroups of interest: patients with preexisting CHD[117] and patients with diabetes mellitus.[131]

Patients with Preexisting Coronary Heart Disease

One parallel arm RCT (102 eligible participants) compared high potency statin to mid potency statin in combination with fibrate among patients with preexisting CHD.[117] The study did not report on the comparative effectiveness of fibrate plus statin on long-term benefits as compared to intensification of statin monotherapy for clinical outcomes including mortality, acute coronary events, and revascularization procedures, nor serious adverse events. Given the paucity of studies, we graded the strength of evidence for all outcomes as insufficient (Table 22).

LDL-c

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**
One trial reported on mean percent change in LDL-c among patients with preexisting CHD.[117] Monotherapy lowered LDL-c by 1 percent to 14 percent more than combination therapy. We graded the strength of evidence as insufficient.

HDL-c

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**
One trial reported on mean percent change in HDL-c among patients with preexisting CHD.[117] Combination therapy with atorvastatin raised HDL-c by 4 percent to 24 percent more than cmonotherapy. Combination therapy with simvastatin raised HDL-c 16 percent more than atorvastatin monotherapy; however, simvastatin monotherapy produced a 3 percent greater increase in HDL-c as compared to this combination. We graded the strength of evidence as insufficient.

Total Cholesterol: HDL Ratio

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**
One trial reported on mean percent change in total cholesterol:HDL ratio among patients with preexisting CHD.[117] At 12 weeks, total cholesterol:HDL decreased by 14 percent in the atorvastatin monotherapy arm and by 17 percent in simvastatin monotherapy arm. In the two combination therapy arms, total cholesterol:HDL decreased by 23 percent (combination with mid potency atorvastatin) and 16 percent (combination with mid potency simvastatin).[117]

Elevated Liver Transaminases

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**

One trial reported on occurrence of elevated liver transaminases among patients with preexisting CHD.[117] At 12 weeks, there was no significant elevations of AST and/or ALT greater than 3 times the upper limit of normal found in any arm.

Adverse Musculoskeletal Events

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**

One trial reported on myalgia among patients with preexisting CHD.[117] At 12 weeks, there were no reported cases on myalgia in the atorvastatin monotherapy arm and 2 cases in simvastatin monotherapy arm. There were no cases in either mid potency statin combination therapy arms.

Patients with Diabetes Mellitus

One parallel arm RCT (437 eligible participants) compared mid potency statin to low potency statin in combination with fibrate.[131] The study did not report on the comparative effectiveness of fibrate plus statin on long-term benefits as compared to intensification of statin monotherapy for mortality or revascularization procedures. Given the paucity of studies, we graded the strength of evidence for all outcomes as insufficient (Tables 23).

Acute Coronary Events

***Low* potency statin combination therapy versus *mid* potency statin monotherapy**

One trial reported on acute coronary events among patients with DM.[131] At 24 weeks, no cases of MI occured in the monotherapy arm and one MI occured in combination therapy arm.

Cerebrovascular Disease

***Low* potency statin combination therapy versus *mid* potency statin monotherapy**

One trial reported on cerebrovascular events among patients with DM.[131] At 24 weeks, one TIA occurred in the monotherapy arm and no events in the combination therapy arm.

Serious Adverse Events

***Low* potency statin combination therapy versus *mid* potency statin monotherapy**

One trial reported on serious adverse events among patients with DM.[131] At 24 weeks, one serious adverse event in each arm (1% of patients).

LDL-c

***Low* potency statin combination therapy versus *mid* potency statin monotherapy**

One trial reported the mean percent LDL-c change among patients with DM.[131] Monotherapy decreased LDL-c 2 percent more than combination therapy, which was not a significant between group difference. This trial also reported proporiton of patient that achieve an LDL-c <100 mg/dL. Interestingly, 6 percent more patients in the combination arm attained this LDL-c goal as compared to the monotherapy group at 12 weeks followup.

HDL-c

***Low* potency statin combination therapy versus *mid* potency statin monotherapy**

One trial reported the mean percent HDL-c change among patients with DM.[131] Combination therapy significantly raised HDL-c 4 percent more than the monotherapy arm.

Non-HDL-c

***Low* potency statin combination therapy versus *mid* potency statin monotherapy**

One trial reported the mean percent non-HDL-c change among patients with DM.[131] Combination therapy decreased non-HDL-c 6 percent more than monotherapy.

Triglycerides

***Low* potency statin combination therapy versus *mid* potency statin monotherapy**

One trial reported the mean percent change in triglycerides among patients with DM.[131] Combination therapy lowered triglycerides 31 percent more than monotherapy at 12 weeks.

Adherence

***Low* potency statin combination therapy versus *mid* potency statin monotherapy**

One trial reported on adherence among patients with DM.[131] At 12 weeks, the trial reported 98 percent treatment adherence in the mid potency statin monotherapy arm and 99 percent treatment adherence in the low potency statin combination arm. In this trial, adherence to medication was defined >80 percent compliance.[131]

Any Adverse Event

***Low* potency statin combination therapy versus *mid* potency statin monotherapy**

One trial reported the occurrence of at least one adverse event among patients with DM.[131] At 12 weeks, the trial reported 15 percent of participants in the monotherapy arm and 17 percent in the combination therapy arm had at least one adverse event.

Musculoskelatal Adverse Events

***Low* potency statin combination therapy versus *mid* potency statin monotherapy**

One trial reported on the occurrence of CPK elevations among patients with DM.[131] There were no cases of CPK elevations >10 times ULN in either arm.

Acute Kidney Injury

***Low* potency statin combination therapy versus *mid* potency statin monotherapy**

One trial reported the occurrence of acute kidney injury among patients with DM.[131] There were no cases in either arm.

Table 20: Low potency statin in combination with fibrate as compared to high potency statin monotherapy in general populations: strength of evidence domains and summary of key findings

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long Term Benefits and Serious Adverse Events								
Mortality	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Acute Coronary Events	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Serious Adverse Events	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Surrogate Clinical Outcomes								
LDL-c	1 (396)	Low [Jadad score 3]	Indirect [Calculated]	NA	Precise	None detected None	High potency statin monotherapy lowered LDL-c 6-11% more than combination arms at 12 months.	Insufficient
HDL-c	1 (396)	Low [Jadad score 3]	Direct [Measured]	NA	Precise	None detected None	Low potency combination therapy raises HDL-c by 9-11% more than high potency statin monotherapy at 12 months.	Insufficient

NA =not applicable

Table 21: Mid potency statin in combination with fibrate as compared to high potency statin monotherapy in general populations: strength of evidence domains and summary of key findings

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long Term Benefits and Serious Adverse Events								
Mortality	1 (356)	Low	Direct	NA	Imprecise	None detected None	No difference between groups	Insufficient
Acute Coronary Events	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Serious Adverse Events	1 (356)	Low	Direct	NA	Imprecise	None detected	No events in the montherapy arm; 0.8% to 3.4% of patients with events in two combination arms	Insufficient
Surrogate Clinical Outcomes								
LDL-c	6 (1666)	Moderate [2 trials with High risk]	Direct [Calculated in 1 trial]	Consistent [6 comparisons favor monotherapy; 2 comparisons favor combination therapy]	Precise	None detected None	High potency statin monotherapy lowers LDL-c by 8% to 15% more than combination therapy at 12 weeks.	Moderate
HDL-c	6 (1503)	Moderate [2 trials with High risk]	Direct [Measured in all trials]	Consistent [All comparisons favor combination therapy]	Precise	None detected None	Combination therapy raises HDL 4% to10% more than high potency stain monotherapy at 12 weeks	Moderate

NA not applicable

Table 22: Mid potency statin in combination with fibrate as compared to high potency statin monotherapy among patients with CHD: strength of evidence domains and summary of key findings

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long Term Benefits and Serious Adverse Events								
Mortality	None	N/A	N/A	NA	NA	NA NA	No eligible studies	Insufficient
Acute Coronary Events	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Serious Adverse Events	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Surrogate Clinical Outcomes								
LDL-c	1 (102)	High [Jadad<3]	Direct [Measured]	N/A	Imprecise	None detected None	Monotherapy lowered LDL-c by 1% to 14% percent more than combination therapy	Insufficient
HDL-c	1 (102)	High [Jadad<3]	Direct [Measured]	N/A	Imprecise	None detected None	Combination therapy raised HDL-c by 4% to 24% more than atorvastatin monotherapy	Insufficient

CHD coronary heart disease; NA not applicable

Table 23: Low potency statin in combination with fibrates as compared to mid potency statin monotherapy among patients with diabetes mellitus: strength of evidence domains and summary of key findings

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long Term Benefits and Serious Adverse Events								
Mortality	1 (291)	Low	Direct	NA	Imprecise	None detected None	No reported deaths in both arms	Insufficient
Acute Coronary Events	1 (291)	Low	Direct	NA	Imprecise	None detected None	No difference between groups	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Serious Adverse Events	1 (291)	Low	Direct	NA	Precise	None detected None	No difference between groups	Insufficient
Surrogate Clinical Outcomes								
LDL-c	1 (291)	Low	Direct	N/A	Precise	None detected None	Monotherapy decreased LDL-c 2% more than combination therapy	Insufficient
HDL-c	1 (291)	Low	Direct	N/A	Precise	None detected None	Combination therapy significantly raised HDL-c 4 % more than monotherapy	Insufficient

NA =not applicable

Combined Lipid-Modifying Therapy with Statin and Niacin versus Intensification of Statin Monotherapy

Study Characteristics

We included seven trials (876 participants in eligible arms) that compared niacin plus statin to intensification of statin monotherapy. All trials were parallel arm randomized controlled trials that took place in North America.[85,94,99,100,125,126,133] All trials were multicenter, except for one single center trial.[133] Eligibility criteria were similar across all trials. All trials included a dietary run in, followed by treatment ranging from 6 weeks to 52 weeks in duration. Four trials compared mid potency statin in combination therapy to high potency statin monotherapy.[85,94,99,100] The other three trials compared low potency statin in combination therapy to mid potency statin monotherapy.[125,126,133] (Appendix E Evidence Tables)

Population Characteristics

In six trials,[94,99,100,125,126,133] the average participant was in their 50s with the mean age ranging from 49-61 years. In the other trial, the study's average participant was in their 70s.[85] Female participants varied between trials and ranged from 24-79 percent in each arm. Race was reported in most trials, and the majority of participants were white (range 61-96% of participants in included arms). The arms in one trial differed significantly by race.[85] Smoking status, prior cardiovascular disease, revascularization events, and diabetes were not consistently reported across trials. When reported, no significant between group differences existed in the trials.[99,125,133] (Appendix E Evidence Tables)

Interventions

Four trials compared mid potency statin in combination with extended release niacin to high potency statin monotherapy.[94,99,100] These monotherapy arms used atorvastatin, rosuvastatin, and simvastatin, and the combination arms used lovastatin, simvastatin, or rosuvastatin. Three trials compared mid potency statin monotherapy to low potency statin in combination with niacin.[125,126,133] All these trials used lovastatin as the statin in both the monotherapy and combination therapy arms. Across all trials, patients had their dose of niacin titrated up over the study period with the final doses ranging from 1g to 2.5g.

Outcomes

Key Points

- **Long-Term Benefits**
    - There is insufficient evidence to compare the long-term benefits of combined lipid-modifying therapy with niacin and statin to intensification of statin monotherapy at any statin potencies.
- **Serious Adverse Events**
    - There is insufficient evidence to compare the serious adverse events of combined lipid-modifying therapy with niacin and statin to intensification of statin monotherapy at any statin potencies.
- **Surrogate Outcomes**

- High potency statin monotherpy is more effective than a mid potency statin in combination with niacin for lowering LDL-c (SOE: low). There is insufficient evidence within other potency comparisons.
- A mid potency statin monotherpy with niacin is more effective than high potency statin monotherapy for raising HDL-c (SOE: low).
- A low potency statin monotherpy with niacin is more effective than mid potency statin monotherapy for raising HDL-c (SOE: moderate).
- There is insufficient evidence to evaluate the effectiveness of combinated lipid-modifying therapy with niacin and statin at lowering total cholesterol:HDL ratio as compared to intensification of statin monotherapy at any statin potencies.

- **Adherence**
  - There is insufficient evidence to compare medication adherence between combined lipid-modifying therapy with niacin and statin to intensification of statin monotherapy at any statin potencies.
- **Short-Term Side Effects**
  - There is insufficient evidence to compare the rates of adverse events between combined lipid-modifying therapy with niacin and statin to intensification of statin monotherapy at any statin potencies.
  - The evidence suggests that there is no difference in the rates of elevated liver transaminases between combined lipid-modifying therapy with niacin and mid potency statin to high potency statin monotherapy. There is insufficient evidence within other potency comparisons.
  - There is insufficient evidence to compare the rates of adverse musculoskeletal events between combined lipid-modifying therapy with niacin and statin to intensification of statin monotherapy at any statin potencies.
- **Subgroups**
  - There is insufficient evidence to compare the long-term benefits of combined lipid-modifying therapy with niacin and statin to intensification of statin monotherapy at any statin potencies among any subgroup.
  - There is insufficient evidence to compare the harms of combined lipid-modifying therapy with niacin and statin to intensification of statin monotherapy at any statin potencies among any subgroup.

Long-term benefits and serious adverse events (KQ1)

Few studies reported on the comparative effectiveness of niacin plus statin on long-term benefits as compared to intensification of statin monotherapy among adults. We graded the strength of evidence for mortality, acute coronary events, revascularization procedures, and serious adverse events as insufficient (Tables 24). We identified no studies that compared low potency statin combination therapy to high potency statin monotherapy.

Mortality

Mid ***potency statin combination therapy versus*** ***high*** ***potency statin monotherapy***
No studies reported deaths.

Low potency ***statin combination therapy versus*** ***mid*** ***potency statin monotherapy***

One study reported the number of deaths during the trial.[125] There was one death in both the mid potency statin monotherapy arm and the low potency statin combination arm; both were considered vascular deaths.

Acute Coronary Events

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**

One study evaluated counts of ACS events during the 12-month study period.[85] One ACS event occurred in the monotherapy arm, while there were no events in the combination therapy arm. There was no between group difference reported.

***Low* potency statin combination therapy versus *mid* potency statin monotherapy**

No studies reported on acute coronary events.

Cerebrovascular Disease

No studies reported on cerebrovascular events.

Revascularization Procedures

No studies reported on revascularization procedures.

Serious Adverse Events

No studies reported on serious adverse events.

Surrogate outcomes, short-term side effects and adherence (KQ2)

All included RCTs evaluated surrogate outcomes including LDL-c and HDL-c. In several RCTs, medication adherence and short-term side effects were evaluated including elevated liver transaminases and elevated creatinine phosphokinase. We identified no studies that compared high potency statin monotherapy to low potency statin combination therapy. We identified no eligible non-randomized extensions of RCTs or FDA reports.

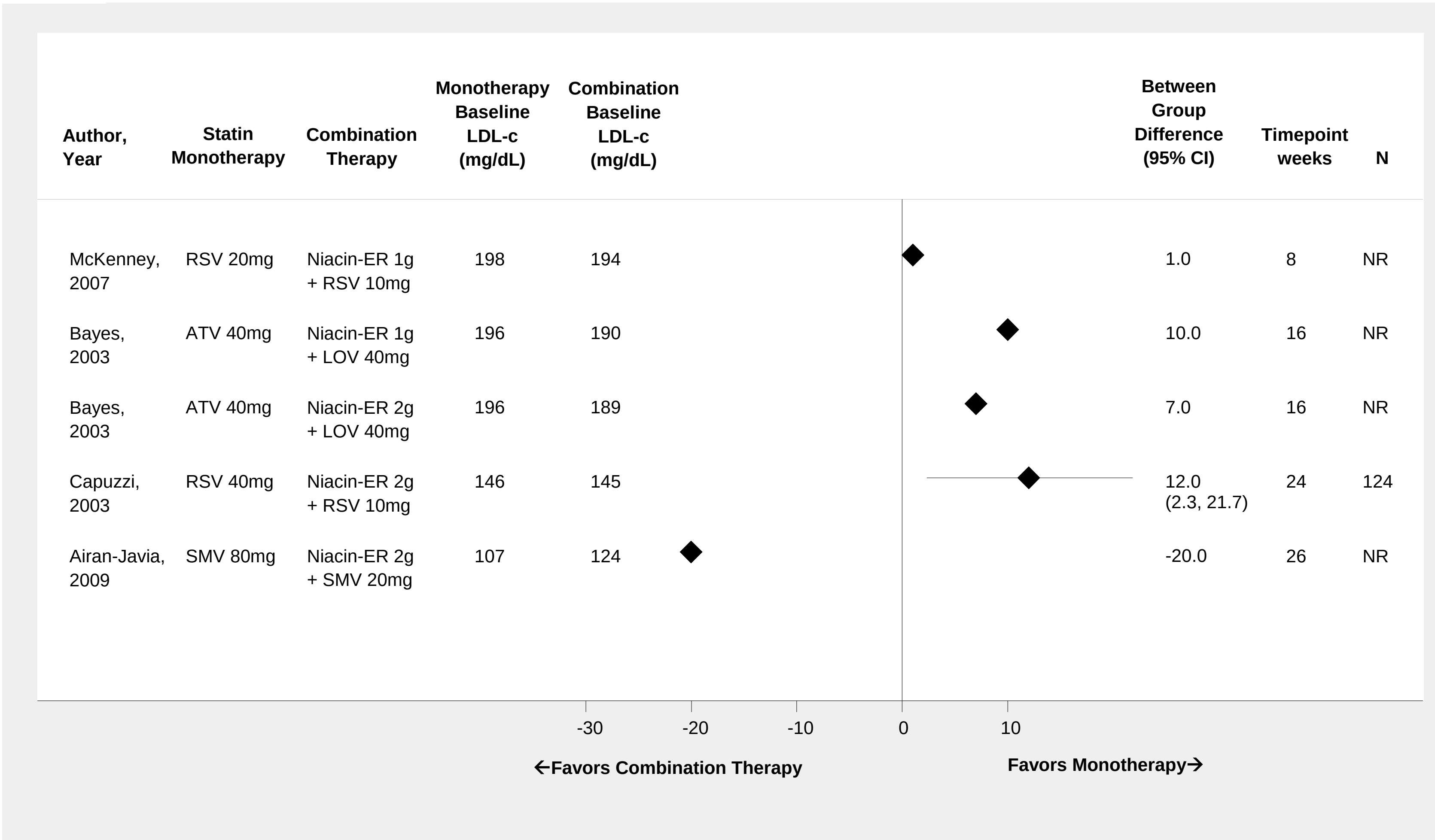
LDL-c

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**

Four trials reported mean percent change in LDL-c (7 comparisons).[85,94,99,100] In three trials, four comparisons favored monotherapy for lowering LDL-c (1 percent to 12 percent greater decrease) as compared to combination therapy.[94,99,100] In one trial, one comparison found no difference between monotherapy and combination therapy for lowering LDL-c.[99] Finally, two comparisons reported in two trials favored combination therapy for lowering LDL-c (3 percent to 22 percent greater decrease) as compared to monotherapy.[85,99]

The results of most comparisons favored monotherapy for lowering LDL-c (Figure 19). The trial that strongly trial favored combination therapy[85] differs from the other trials in several ways. First, patients had to have hyperlipidemia and at least 30 percent carotid stenosis on ultrasound to be included, whereas all other trials recruited patients based only on have hyperlipidemia. Second, the baseline LDL values in this trial were much lower than the other trials, as there was no washout of prior lipid-lowering medications. Finally, the baseline LDL value in the monotherapy arm was lower (median 107 mg/dL) than the combination therapy arm (124mg/dL). All three of these factors may explain the different results in this trial. We graded the strength of evidence as low (Table 24). While four trials reported on this comparison, only two of the trials reported or provided sufficient information for us to calculate SE for the LDL-c difference in differences. Therefore, we did not perform meta-analysis.

Figure 19: Mean difference in percent LDL change from baseline to time point comparing mid potency combination therapy with niacin to high potency monotherapy



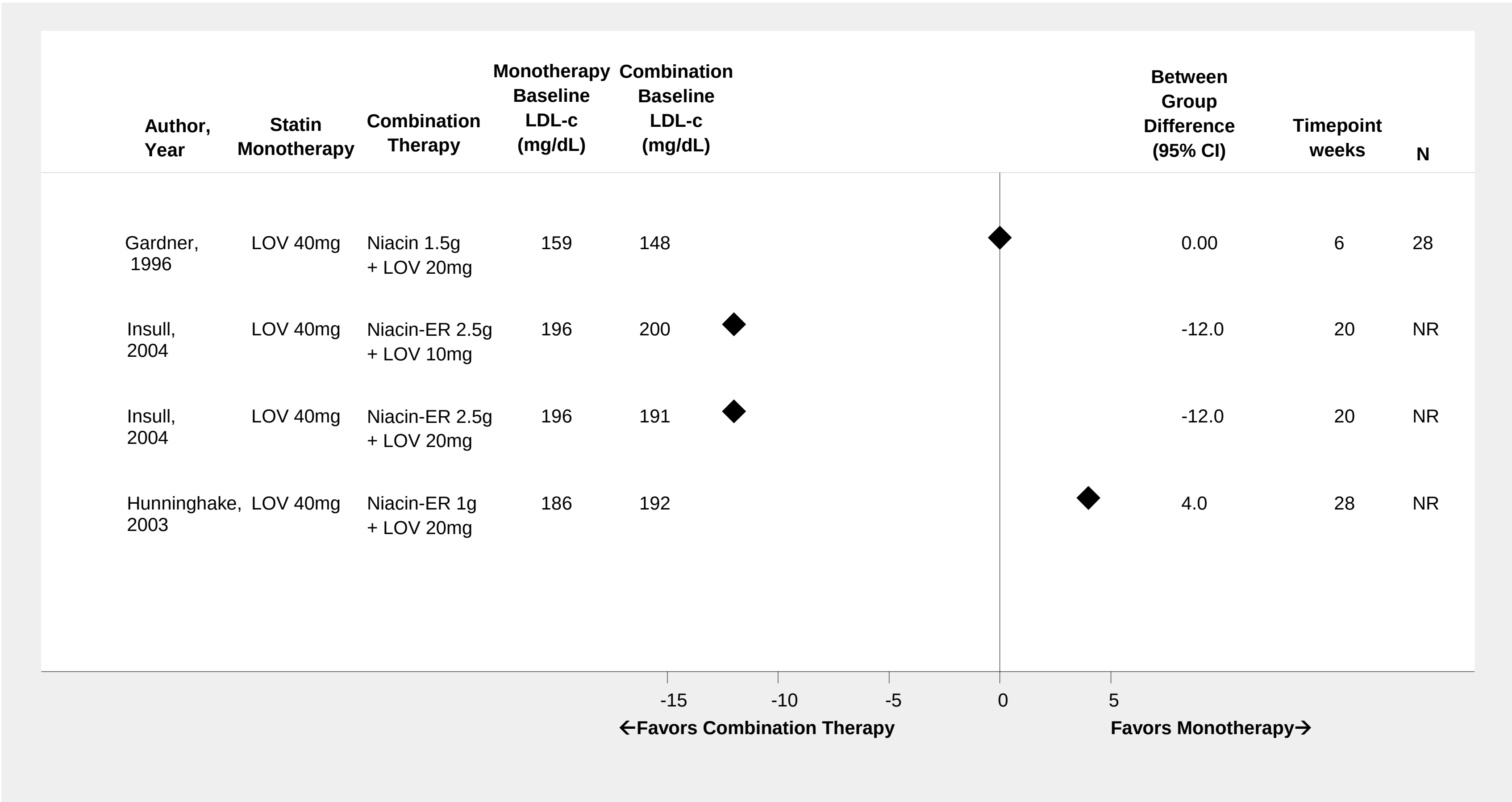
ATV =atrovastatin; RSV= rosuvastatin; SMV= simvastatin; LOV= Lovastatin; ER= extended release; NR= not reported
For diamonds without confidence intervals, SE/SD could not be calculated

<u>Low</u> potency statin combination therapy versus <u>mid</u> potency statin monotherapy

Three trials reported mean percent LDL-c change.[125,126,133] Overall, the effects on LDL-c were variable. At 6 weeks,[133] one trial found that both the statin monotherapy arm and combination arm reduced LDL-c by 8 percent. At 20 weeks,[126] another trial found that the two combination arms each reduced LDL-c 12 percent more than the statin monotherapy arm. At 28 weeks, the final trial found that monotherapy decreased LDL-c 4 percent more than combination therapy.[125]

The results did not favor either mid potency statin monotherapy or low potency statin in combination with niacin for lowering LDL-c (Figure 20). In one trial that favored combination therapy,[126] investigators used higher doses of niacin-ER (2.5g) than the other trial that favored statin monotherapy (niacin-ER 1g).[125] This difference in niacin dose may explain the difference in LDL effect among these trials. We graded the strength of evidence as insufficient (Table 25). While three trials reported on this comparison, only one of the trials reported or provided sufficient information for us to calculate SE for the LDL-c difference in differences. Therefore, we did not perform meta-analysis.

Figure 20: Mean difference in percent LDL change from baseline to time point comparing low potency combination therapy with niacin to mid potency monotherapy



LOV= lovastatin; ER= extended release; NR =not reported
For diamonds without confidence intervals, SE/SD could not be calculated

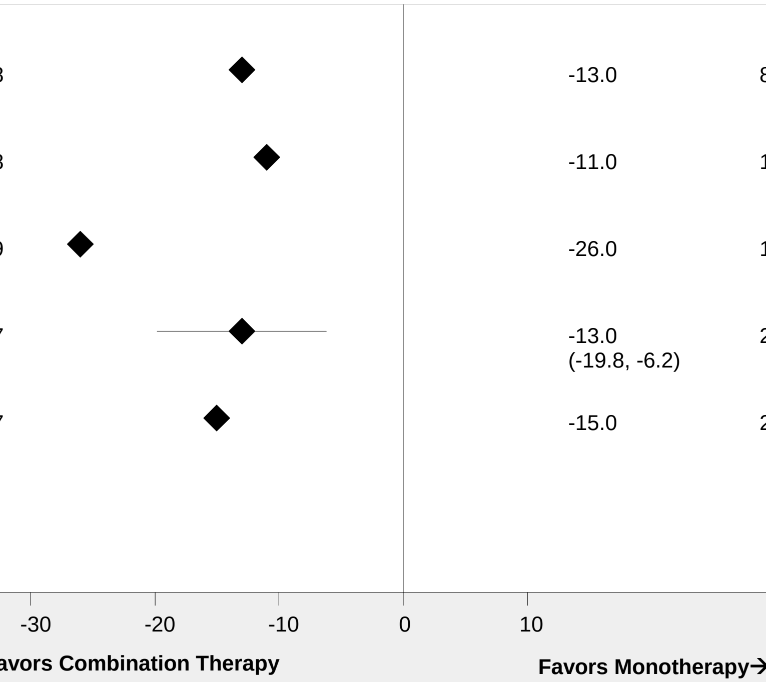
HDL-c

Mid potency statin combination therapy versus high potency statin monotherapy

Four trials reported mean percent change in HDL-c.[85,94,99,100] All trials favored combination therapy in raising HDL-c (11 percent to 26 percent greater increase) as compared to monotherapy (Figure 21). Treatment duration ranged from 8 weeks to 12 months. We graded the strength of evidence as low. While four trials reported on this comparison, only two of the trials reported or provided sufficient information for us to calculate SE for the HDL-c difference in differences. Therefore, we did not perform meta-analysis.

Figure 21: Mean difference in percent HDL change from baseline to time point comparing mid potency combination therapy with niacin to high potency statin monotherapy

Author, Year	Statin Monotherapy	Combination Therapy	Monotherapy Baseline HDL-c (mg/dL)	Combination Baseline HDL-c (mg/dL)	Between Group Difference (95% CI)	Timepoint weeks	N
McKenney, 2007	RSV 20mg	Niacin-ER 1g + RSV 10mg	49	48	-13.0	8	NR
Bayes, 2003	ATV 40mg	Niacin-ER 1g + LOV 40mg	38	38	-11.0	16	NR
Bayes, 2003	ATV 40mg	Niacin-ER 2g + LOV 40mg	38	39	-26.0	16	NR
Capuzzi, 2003	RSV 40mg	Niacin-ER 2g + RSV 10mg	35	37	-13.0 (-19.8, -6.2)	24	124
Airan-Javia, 2009	SMV 80mg	Niacin-ER 2g + SMV 20mg	41	47	-15.0	26	NR

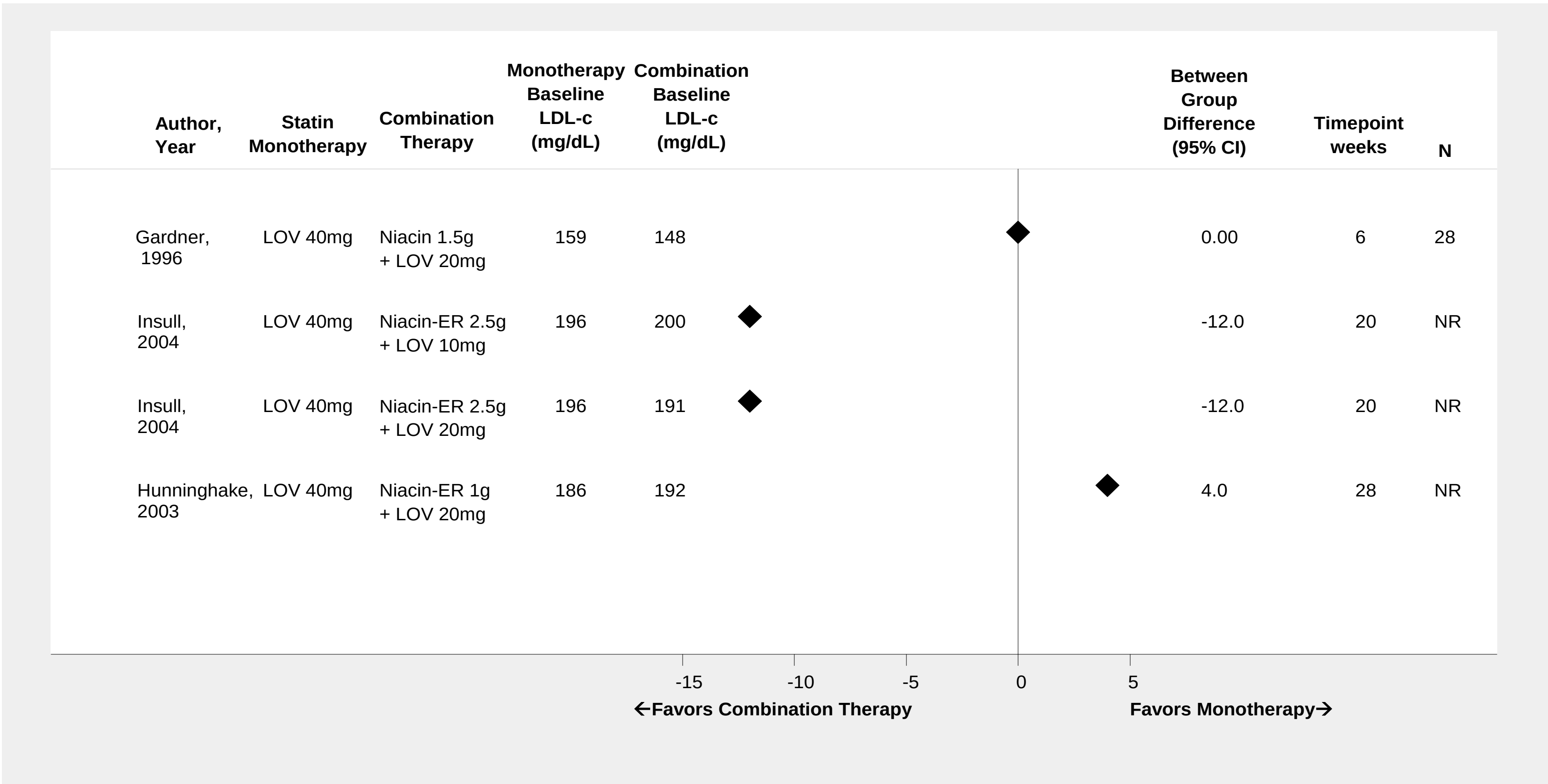


ATV atrovastatin; ER extended-release; RSV rosuvastatin; SMV simvastatin; NR not reported
For diamonds without confidence intervals, SE/SD could not be calculated

***Low* potency statin combination therapy versus *mid* potency statin monotherapy**

Three trials reported mean percent change in HDL-c.[125,126,133] All trials favored combination therapy in raising HDL-c (15 percent to 27 percent greater increase) as compared to monotherapy . We graded the strength of evidence as moderate (Table 23). While three trials reported on this comparison, only one of the trials reported or provided sufficient information for us to calculate SE for the HDL-c difference in differences (Figure 22). Therefore, we did not perform meta-analysis.

Figure 22: Mean difference in percent LDL change from baseline to time point comparing low potency combination therapy with niacin to mid potency statin monotherapy



LOV lovastatin; ER extended release; NR not reported
For diamonds without confidence intervals, SE/SD could not be calculated

Total Cholesterol:HDL

Mid potency statin combination therapy versus high potency statin monotherapy

Only one trial reported the mean percent change in total cholesterol:HDL ratio.[94] Combination therapy lowered total cholesterol:HDL 5 percent more than monotherapy. This difference was not statistically significantly different.

Low potency statin combination therapy versus mid potency statin monotherapy

No studies reported mean percent change in total cholesterol:HDL ratio.

Atherosclerosis

No studies reported on atherosclerosis.

Adherence

Mid potency statin combination therapy versus high potency statin monotherapy

Two trials reported on treatment adherence.[99,100] In one trial, adherence was ≥94 percent in all arms at 16 weeks.[99] The other trial reported lower adherence at 24 weeks, with less than 50 percent of combination arm participants adhering to their medications.[100]

Low potency statin combination therapy versus mid potency statin monotherapy

One trial reported on treatment adherence.[126] Adherence to medications was 96 percent in both arms at 20 weeks.

Any Adverse Event

Mid potency statin combination therapy versus high potency statin monotherapy

One trial reported the number of participants who experienced at least one adverse event.[100] In this study, 28 percent of participants in the monotherapy arm and 53 percent of participants in the combination therapy arm had at least one adverse event over the 24-week study period (calculated p=0.16).

Low potency statin combination therapy versus mid potency statin monotherapy

One trial reported the number of participants who experienced at least one adverse event.[126] In the statin monotherapy arm, 52 percent of participants had at least one adverse event, while 44 percent in one combination arm (N-ER 2.5g + LOV 10mg) and 62 percent in the other combination arm (N-ER 2.5g + LOV 20mg) had at least one adverse event during the 20-week study period. Calculated p-values for these comparisons were not significant.

Withdrawal due to Adverse Events

Mid potency statin combination therapy versus high potency statin monotherapy

No studies reported withdrawals due to adverse events.

Low potency statin combination therapy versus mid potency statin monotherapy

One trial reported the number of participants who withdrew from the study due to an adverse event.[125] At 28 weeks, 19 percent of participants in the mid potency statin monotherapy arm and 10 percent in the low potency statin combination arm withdrew due to an adverse event, which was not significantly different.

Cancer

No studies reported on cancer.

Elevated Liver Transaminases

Mid potency statin combination therapy versus high potency statin monotherapy

Three trials reported on significant elevations in AST and/or ALT.[85,99,100] There were no reported cases of elevated AST and/or ALT greater than 3 times the ULN in two trials.[99,100] One trial reported that 1 participant experienced liver transaminase elevations in the high potency statin monotherapy arm and no cases in the mid potency statin combination arm.[85] Overall, there appears to be no difference in the rates of elevated liver transaminases between combined lipid-modifying therapy with niacin and mid potency statin to high potency statin monotherapy.

Low potency statin combination therapy versus mid potency statin monotherapy

Two trials reported on significant elevations in AST and/or ALT.[125,126] There were two cases of elevated AST and/or ALT greater than 3 times the ULN at 20 weeks in one trial, one in each combination arm (N-ER 2.5g + LOV 10mg and N-ER 2.5g + LOV 20mg).[126] While there was one case of elevated AST and/or ALT greater than 3 times the ULN in the statin monotherapy arm at 28 weeks in the other trial.[125]

Adverse Musculoskelatal Events

Mid potency statin combination therapy versus high potency statin monotherapy

Two trials reported on occurrences of myalgia.[85,100] At 24 weeks, 7 percent of participants in the monotherapy arm and 1 percent of participants in the combination arm reported myalgia. The other trial reported 2 cases of muscle cramping in the high potency statin monotherapy arm and no cases in the mid potency combination arm.[85]

Two trials reported on elevations of CPK.[99,100] One trial reported on CPK elevations greater than 5 times the ULN at 16 weeks,[99] while the other reported on CPK elevations greater than 10 times the ULN at 24 weeks.[100] No cases of CPK elevations were identified in either trial.

Low potency statin combination therapy versus mid potency statin monotherapy

One trial reported on occurrences of myalgia.[125] At 28 weeks, 7 percent of participants in the monotherapy arm and 4 percent in the combination arm reported muscle aches.

Two trials reported on elevations of CPK.[125,126] One trial reported on CPK elevations greater than 3 times the ULN at 20 weeks,[126] while the other reported on CPK elevations greater than 10 times the ULN at 28 weeks.[125] No cases of CPK elevations were identified in either trial.

New Onset Diabetes Mellitus

Mid potency statin combination therapy versus high potency statin monotherapy

No studies compared any diabetes-related outcomes.

Low potency statin combination therapy versus mid potency statin monotherapy

Two trials reported on hyperglycemia.[125,126] At 20 weeks, there were no cases of hyperglycemia in the statin monotherapy arm, while 6 percent and 3 percent of patients in the combination therapy arms (N-ER 2.5g + LOV 10mg and N-ER 2.5g + LOV 20mg, respectively) experienced hyperglycemia.[126] In the other trial, 7 percent of monotherapy arm participants and

4 percent of combination arm participants had fasting glucose elevated greater than 1.3 times the ULN at 28 weeks.[125]

Acute Kidney Injury

No studies reported on acute kidney injury.

Subgroups of patients (KQ3)

No studies reported on the comparative effectiveness of niacin plus statin on benefits or harms as compared to intensification of statin monotherapy among subgroups.

Table 24: Mid potency statin in combination with niacin as compared to high potency statin monotherapy in <u>general populations</u>: strength of evidence domains and key findings

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long Term Benefits and Serious Adverse Events								
Mortality	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Acute Coronary Events	1 (50)	Low [Double blind; low attrition]	Direct	NA	Imprecise	None detected None	One ACS event in the high potency monotherapy arm and no events in the combination arm at 12 months.	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Serious Adverse Events	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Surrogate Clinical Outcomes								
LDL-c	4 (629)	High [3 trials with Jadad score<3; 1 trial from 2013 update with low risk of bias]	Indirect [LDL calculated in 2 trials]	Consistent [4 comparisons favor statin monotherapy; 1 comparison effect favors combination therapy non-significantly]	Imprecise	None detected None	Most studies favor high potency statin monotherapy by lowering LDL-c up to 12% more than mid potency statin in combination with niacin at 8-26 weeks.	Low
HDL-c	4 (629)	High [3 trials with Jadad score<3; 1 trial from 2013 update with low risk of bias]	Direct [HDL measured in all trials]	Consistent [All comparisons favor combination therapy]	Imprecise	None detected None	All studies favor mid potency combination therapy by raising HDL-c by 11-26% more than high potency statin monotherapy at 8-26 weeks.	Low

HDL=high density lipoprotein; LDL= low density lipoprotein; NA =not applicable

Table 25: Low potency statin in combination with niacin as compared to mid potency statin monotherapy in <u>general populations</u>: strength of evidence domains and key findings

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long Term Benefits and Serious Adverse Events								
Mortality	1 (118)	Low [Jadad score≥3]	Direct	NA	Imprecise	None detected None	One death in the mid potency statin monotherapy group and one death in the low potency statin in combination with niacin group at 28 weeks.	Insufficient
Acute Coronary Events	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Serious Adverse Events	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Surrogate Clinical Outcomes								
LDL-c	3 (247)	Low [1 trial with Jadad score<3]	Indirect [LDL calculated in 2 trials]	Inconsistent [1 comparison favors monotherapy; 2 comparisons favor combination therapy; 1 comparison with no difference]	Imprecise	None detected None	Three studies show no consistent effect in LDL-c reduction between mid potency statin montherapy and low potency statin in combination with niacin at 6-28 weeks.	Insufficient
HDL-c	3 (247)	Low [1 trial with Jadad score<3]	Direct [HDL measured in all trials]	Consistent [All trials favor combination therapy]	Imprecise	None detected None	All studies favor low potency combination therapy by raising HDL-c by 15-27% more than mid potency statin monotherapy at 6-28 weeks.	Moderate

HDL=high density lipoprotein; LDL= low density lipoprotein; NA= not applicable

Combined Lipid-Modifying Therapy with Statin and Omega-3 Fatty Acid versus Intensification of Statin Monotherapy

Study Characteristics

We included two trials (99 participants in eligible arms) comparing omega-3 plus statin to intensification of statin monotherapy.[111,112,114] The results of these two studies were reported in 3 articles. Both trials were parallel arm randomized controlled trials that took place in single centers. Both trials took place in Greece.[111,112,114] The treatment duration in both trials was 3 months, and each included one relevant comparison of high potency statin monotherapy to mid potency statin in combination therapy. (Appendix E Evidence Tables)

Population Characteristics

The average participant was in their 50s and the majority were women in all eligible arms.[111,112,114] The percentage of current smokers in the arms ranged from 28-53 percent. Race, prior cardiovascular disease, revascularization events, and diabetes were not reported. No significant between group differences existed in either trial. (Appendix E Evidence Tables)

Interventions

In both trials,[111,112,114] the combination arm included omega-3 fatty acid 2g + rosuvastatin 10mg and the statin monotherapy arm included rosuvastatin 40mg. The omega-3 fatty acid contained 465mg of EPA and 375mg of DHA.

Outcomes

Key Points

- **Long-Term Benefits**
  - There is insufficient evidence to compare the long-term benefits of combined lipid-modifying therapy with omega-3 and statin to intensification of statin monotherapy.
- **Serious Adverse Events**
  - There is insufficient evidence to compare the serious adverse events of combined lipid-modifying therapy with omega-3 and statin to intensification of statin monotherapy.
- **Surrogate Outcomes**
  - There is insufficient evidence to evaluate the effectiveness of combined lipid-modifying therapy with omega-3 and statin at lowering LDL as compared to intensification of statin monotherapy.
  - There is insufficient evidence to evaluate the effectiveness of combined lipid-modifying therapy with omega-3 and statin at raising HDL as compared to intensification of statin monotherapy.
- **Short-Term Side Effects**
  - There is insufficient evidence to compare the rates of elevated liver transaminases between combined lipid-modifying therapy with omega-3 and statin to intensification of statin monotherapy.

- There is insufficient evidence to compare the rates of elevated creatinine phosphokinase between combined lipid-modifying therapy with omega-3 and statin to intensification of statin monotherapy.

- **Adherence**
  - There is insufficient evidence to compare medication adherence between combined lipid-modifying therapy with omega-3 and statin to intensification of statin monotherapy.
- **Subgroups**
  - There is insufficient evidence to compare the long-term benefits of combined lipid-modifying therapy with omega-3 and statin to intensification of statin monotherapy among any subgroup.
  - There is insufficient evidence to compare the harms of combined lipid-modifying therapy with omega-3 and statin to intensification of statin monotherapy among any subgroup.

Long-term benefits and serious adverse events (KQ1)

No study reported on the comparative effectiveness of omega-3 plus statin on long-term benefits as compared to intensification of statin monotherapy among adults. We graded the strength of evidence for mortality, acute coronary events, revascularization procedures, and serious adverse events as insufficient (Table 26).

Surrogate outcomes, short-term side effects and adherence (KQ2)

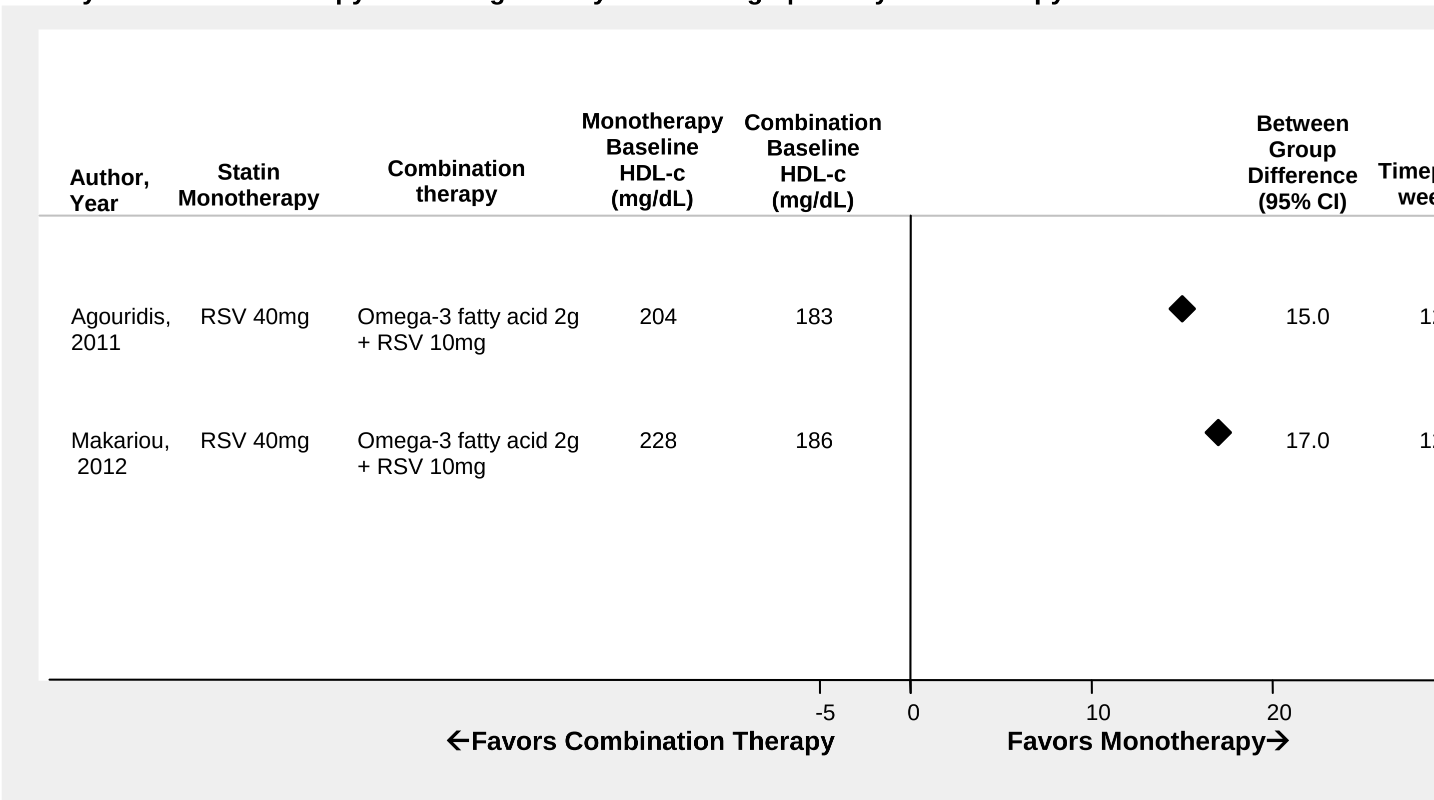
Both trials [111,112,114] evaluated several surrogate outcomes including LDL-c, LDL goal attainment, and HDL-c. Several short-term side effects were evaluated including withdrawal due to an adverse event, elevated liver transaminases and myalgia. Adherence was not assessed in either trial. We identified no studies that compared high potency statin monotherapy to low potency statin combination therapy or mid potency statin monotherapy to low potency statin combination therapy. We identified no eligible non-randomized extensions of RCTs or FDA reports.

LDL-c

Mid potency statin combination therapy versus high potency statin monotherapy

Two trials reported mean percent change in LDL-c at 3 months.[111,112,114] Monotherapy signicantly reduced LDL-c 15 percent to 17 percent more than combination therapy. One also examined LDL goal attainment.[111,112] More monotherapy patients (4 percent) achieve their LDL-c goal as compared to combination therapy patients. While the available evidence favors monotherapy for lowering LDL-c (Figure 23), we graded the strength of evidence as insufficient (Table 26). We did not perform meta-analysis, given the limited number of trials (n=2).

Figure 23: Mean difference in percent LDL change from baseline to time point comparing mid potency combination therapy with omega-3 fatty acids to high potency monotherapy



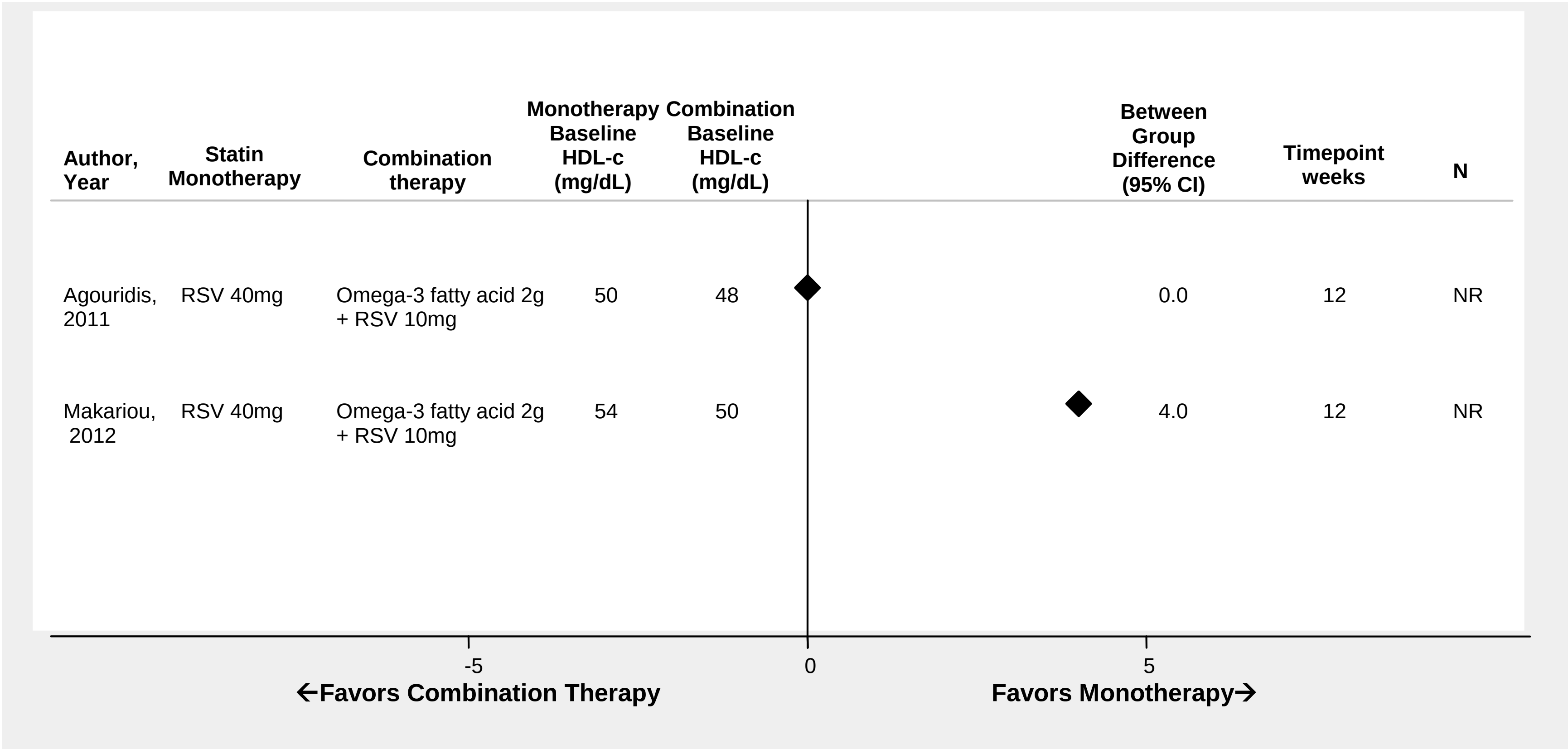
RSV= rosuvastatin; SMV= simvastatin; NR= not reported
For diamonds without confidence intervals, SE/SD could not be calculated

HDL-c

<u>Mid</u> potency statin combination therapy versus <u>high</u> potency statin monotherapy

Two trials reported mean percent change in HDL-c at 3 months.[111,112,114] One trial found no difference between the monotherapy and combination therapy arms (4 percent increase in both arms).[111,112] In the other study, the monotherapy arm increased HDL-c by 1 percent and the combination arm HDL-c by 5 percent at 3 months.[114]The available evidence suggests there is little to no difference between montherapy and combination therapy on HDL-c. We graded the strength of evidence as insufficient, and therefore, did not conduct meta-analysis (Figure 24).

Figure 24: Mean difference in percent HDL change from baseline to time point comparing mid potency combination therapy with omega-3 fatty acid to high potency statin monotherapy



RSV rosuvastatin; NR not reported
For diamonds without confidence intervals, SE/SD could not be calculated

Total Cholesterol:HDL

No studies reported on total cholesterol:HDL ratio.

Atherosclerosis

No studies reported on atherosclerosis.

Adherence

No studies reported on adherence.

Any Adverse Event

No studies reported on the occurrence of any adverse event.

Withdrawal due to Adverse Events

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**

One study reported the number of participants who withdrew from the study due to an adverse event during the 3-month study period.[111,112] No participants in the statin monotherapy arm withdrew due to an adverse event, while 1 participant from the combination therapy arm withdrew due to an adverse event.

Cancer

No studies reported on cancer.

Elevated Liver Transaminases

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**

One trial reported the occurrence of significant elevations in AST and/or ALT.[111,112] In this trial, 1 participant experienced liver transaminase elevations in the combination therapy arm and no cases in the statin monotherapy arm.

Adverse Musculoskelatal Events

***Mid* potency statin combination therapy versus *high* potency statin monotherapy**

One trial reported occurrences of myalgia during the 3-month study period.[111,112] There were no cases of myalgia in either arm.

New Onset Diabetes Mellitus

No studies reported on any diabetes-related outcomes.

Acute Kidney Injury

No studies reported on acute kidney injury events.

Subgroups of patients (KQ3)

No studies reported on the comparative effectiveness of omega-3 plus statin on benefits or harms as compared to intensification of statin monotherapy among subgroups.

Table 26: Mid potency statin in combination with omega-3 fatty acids as compared to high potency statin monotherapy in general populations: strength of evidence domains and summary of key findings

Outcome	No. Studies (N)	Risk of Bias	Directness	Consistency	Precision	Reporting Bias Other Issues	Findings and Magnitude of Effect	Strength of Evidence
Long Term Benefits and Serious Adverse Events								
Mortality	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Acute Coronary Events	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Revascularization Procedures	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Serious Adverse Events	None	NA	NA	NA	NA	NA NA	No eligible studies	Insufficient
Surrogate Clinical Outcomes								
LDL-c	2 (99)	High [Both open label trials, no description of losses to followup]	Indirect [LDL calculated not directly measured in both trials]	Consistent [Both trials favor high potency statin monotherapy]	Imprecise	Not detected None	Two studies that favor high potency statin monotherapy by lowering LDL-c 15-17% more than mid potency statin in combination with omega-3 fatty acid at 3 months.	Insufficient
HDL-c	2 (99)	High [Both open label trials, no description of losses to followup]	Direct [HDL measured in both trials]	Inconsistent [1 trial favors combination therapy, no difference in other trial]	Imprecise	Not detected None	Two studies with little to no difference between combination therapy and statin monotherapy on raising HDL-c (0-4%).	Insufficient

HDL=high density lipoprotein; LDL= low density lipoprotein; NA= not applicable

Discussion

Key Findings and Implications

The evidence suggests that some combination therapy regimens may confer benefits with respect to lowering LDL-c including bile acid sequestrants and ezetimibe. In contrast, intensification of statin monotherapy provided benefits or showed little difference with respect to LDL-c lowering in comparison to combination therapy with fibrates or niacin. LDL-c is an important factor in the development of atherosclerotic cardiovascular disease and higher levels of LDL-c have been associated with greater risk of this disease.[7,8] However, there is insufficient evidence to address whether these LDL-c lowering benefits achieved with these medications translate into decreased rates of atherosclerotic cardiovascular disease. Many trials comparing these combination regimens to statin monotherapy such as ENHANCE, AIM-HIGH, and ACCORD-lipid have demonstrated that combination therapy can lead to superior lipid outcomes, but fails to reduce atherosclerosis or lead to decreased rates of cardiovascular death, MI, revascularization, or stroke.[49,52,54] Most trials included in this report are of relatively short duration (<3 months). In this limited timeframe, investigators are unlikely to capture any changes in a chronic condition like atherosclerotic cardiovascular disease, which typically develops and progresses over a number of years. The strength of evidence for all observed comparisons in general populations is provided in Table 27 and in subgroups in Table 28. Only one comparison was graded as having a high strength of evidence. Nine comparisons were graded as having moderate strength of evidence. All others have low or insufficient evidence.

Table 27: Summary of the strength of evidence for general populations

	Potency Comparisons (combination therapy vs. monotherapy)	Mortality	Acute Coronary Events	Revascularization Procedures	Serious Adverse Events	LDL-c	HDL-c
Bile Acid Sequestrant	Low potency vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Mid potency vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Low potency vs mid potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	**Moderate with combination therapy favored**	Insufficient
Ezetimibe	Low potency vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	**Low with combination therapy favored**	**Low with combination therapy favored**
	Mid potency vs high potency monotherapy	Insufficient	Insufficient	Insufficient	**High with monotherapy favored**	**Moderate with combination therapy favored**	**Low with combination therapy favored**
	Low potency vs mid potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	**Moderate with combination therapy favored**	**Low with combination therapy favored**
Fibrates	Low potency vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Mid potency vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	**Moderate with monotherapy favored**	**Moderate with combination therapy favored**
	Low potency vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Niacin	Low potency vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Mid potency vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	**Low with monotherapy favored**	**Low with combination therapy favored**
	Low potency vs mid potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	**Moderate with combination therapy favored**

	Potency Comparisons (combination therapy vs. monotherapy)	Mortality	Acute Coronary Events	Revascularization Procedures	Serious Adverse Events	LDL-c	HDL-c
Omega-3 Fatty Acid	Low potency vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Mid potency vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Low potency vs mid potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient

HDL=high density lipoprotein; LDL= low density lipoprotein

Table 28: Summary of the strength of evidence for subgroups

Subgroup	Combination Agent	Potency Comparisons (combination therapy vs. monotherapy)	Mortality	Acute Coronary Events	Revascularization Procedures	Serious Adverse Events	LDL-c	HDL-c
Preexisting CHD	Ezetimibe	Low potency vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
		Mid potency vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	**Moderate with combination therapy favored**	**Low with combination therapy favored**
		Low potency vs mid potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Fibrates	Mid potency vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
Diabetes	Ezetimibe	Low potency vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
		Mid potency vs high potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	**Moderate with combination therapy favored**	**Moderate with combination therapy favored**
		Low potency vs mid potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient
	Fibrates	Low potency vs mid potency monotherapy	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient

CHD= coronary heart disease; LDL= low density lipoprotein

Evidence

Combination Therapy with Bile Acid Sequestrant and Statin Compared to Intensification of Statin Monotherapy

Six randomized trials (410 participants) were identified. There is insufficient evidence to compare the benefits of combined lipid-modifying therapy with a bile acid sequestrant and statin to intensification of statin monotherapy on long-term clinical outcomes including mortality, acute coronary events or revascularization procedures, regardless of statin potency. There is insufficient evidence to compare the harms of combined lipid-modifying therapy with a bile acid sequestrant and statin to intensification of statin monotherapy, regardless of statin potency.

Two trials compared mid potency statin in combination with a bile acid sequestrant to high potency statin monotherapy (122 participants). There is insufficient evidence to compare the effects of mid potency statin in combination with a bile acid sequestrant and high potency statin monotherapy on LDL-c or HDL-c. Four trials compared low potency statin in combination with a bile acid sequestrant to mid potency statin monotherapy (288 participants). Low potency statin in combination with a bile acid sequestrant lowers LDL-c up to 14 percent more than mid potency statin monotherapy (SOE: moderate). There is insufficient evidence to compare mid potency statin monotherapy and low potency statin in combination with bile acid sequestrant on HDL-c.

Combination Therapy with Ezetimibe and Statin Compared to Intensification of Statin Monotherapy

Thirty-eight randomized trials (10,955 participants) were identified. There is insufficient evidence to compare the benefits of combined lipid-modifying therapy with ezetimibe and statin to intensification of statin monotherapy on long-term clinical outcomes including mortality, acute coronary events or revascularization procedures, regardless of statin potency.

Twelve trials compared mid potency statin in combination with ezetimibe to high potency statin monotherapy in general populations (5991 participants), while there were 10 trials among patients with coronary heart disease (1050 participants) and 3 trials among diabetic patients (1581 participants). Moderate strength evidence favors mid potency statin in combination with ezetimibe for lowering LDL-c as compared to high potency statin monotherapy among general populations and patients with coronary heart diseaseand patients with diabetes. The evidence also favors a mid potency statin in combination with ezetimibe for raising HDL-c as compared to high potency statin monotherapy in general populations. However, the strength of evidence is high that favors high potency statin monotherapy with respect lower rates of serious adverse effects as compared to mid potency statin in combination with ezetimibe in general populations. Unfortunately, there was insufficient evidence to evaluate harms outcomes among the coronary heart disease and diabetes subgroups. Overall, these findings suggest that mid potency statin in combination with ezetimibe may help patients better achieve their lipid goals, but with potential greater risk of harms.

Twelve trials compared low potency statin in combination with ezetimibe to high potency statin monotherapy (1571 participants). Low strength of evidence favors low potency statin in combination with ezetimibe for lowering LDL-c as compared to high potency statin monotherapy. The evidence also favors a low potency statin in combination with ezetimibe for raising HDL-c as compared to high potency statin monotherapy. There is insufficient evidence to compare the harms of low dose statin in combination with ezetimibe and high potency monotherapy.

Seven trials compared low potency statin in combination with ezetimibe to mid potency statin monotherapy (1195 participants). The strength of evidence is moderate that favors low potency statin in combination with ezetimibe for lowering LDL-c as compared to mid potency statin monotherapy. The evidence also favors a low potency statin in combination with ezetimibe for raising HDL-c as compared to mid potency statin monotherapy. There is insufficient evidence to compare the harms of low dose statin in combination with ezetimibe and mid potency monotherapy.

Combination Therapy with Fibrate and Statin Compared to Intensification of Statin Monotherapy

Eight randomized trials (1824 participants) were identified. There is insufficient evidence to compare the benefits of combined lipid-modifying therapy with fibrate and statin to intensification of statin monotherapy on long-term clinical outcomes including mortality, acute coronary events or revascularization procedures, regardless of statin potency. There is insufficient evidence to compare the serious adverse events of combined lipid-modifying therapy with fibrate and statin to intensification of statin monotherapy, regardless of statin potency.

Six trials compared mid potency statin in combination with fibrate to high potency statin monotherapy (1585 participants). High potency statin monotherapy lowers LDL-c up to 15 percent more than mid potency statin in combination with fibrate (SOE: moderate). However, mid potency statin in combination with fibrate raises HDL-c up to 10 percent more than high potency statin monotherapy (SOE: moderate). The evidence suggests little to no difference with respect to elevated liver transaminase or creatinine phosphokinase levels between these two groups; however, more study withdrawals due to adverse events occurred in the combination therapy than the statin monotherapy group. Overall, these findings suggest that high potency statin monotherapy may help patients better achieve their LDL-c goals with potentially lower risk of harms as compared to mid potency statin in combination with fibrate.

Combination Therapy with Niacin and Statin Compared to Intensification of Statin Monotherapy

Seven randomized trials (876 participants) were identified. There is insufficient evidence to compare the benefits of combined lipid-modifying therapy with niacin and statin to intensification of statin monotherapy on long-term clinical outcomes including mortality, acute coronary events or revascularization procedures, regardless of statin potency.

Four trials compared mid potency statin in combination with niacin to high potency statin monotherapy (629 participants). High potency statin monotherapy lowers LDL-c up to 12 percent more than mid potency statin in combination with niacin (SOE: low). In contrast, mid potency statin in combination with niacin for raises HDL-c up to 26 percent more than high potency statin monotherapy (SOE: low). The evidence suggests no difference in rates of elevated liver transaminases for this comparison.

Three trials compared low potency statin in combination with niacin to mid potency statin monotherapy (247 participants). The strength of evidence is insufficient to compare a low potency statin in combination with niacin and mid potency statin monotherapy at lowering LDL-c. However, low potency statin in combination with niacin raises HDL-c up to 27 percent more than mid potency statin monotherapy (SOE: moderate). There is insufficient evidence to compare the harms of combined lipid-modifying therapy with a low potency statin in combination with niacin to mid potency statin monotherapy.

Combination Therapy with Omega-3 Fatty Acid and Statin Compared to Intensification of Statin Monotherapy

Two randomized trials (99 participants) were identified, which both compared a mid potency statin in combination with omega-3 fatty acid to high potency statin monotherapy. There is insufficient evidence to compare the benefits of combined lipid-modifying therapy with an omega-3 fatty acid and statin to intensification of statin monotherapy on long-term clinical outcomes including mortality, acute coronary events or revascularization procedures, regardless of statin potency. There is insufficient evidence to compare the harms of combined lipid-modifying therapy with an omega-3 fatty acid and statin to intensification of statin monotherapy, regardless of statin potency. Given the limited number of trials, the strength of evidence is insufficient to evaluate the effectiveness of combined lipid-modifying therapy with omega-3 and statin at lowering LDL-c or raising HDL-c as compared to intensification of statin monotherapy. However, the available evidence favors high potency statin monotherapy for lowering LDL-c and suggests that there is little difference between high potency statin monotherapy and mid potency statin in combination with omega-3 fatty acid on raising HDL-c.

Important Unanswered Questions

Which of the Key Questions Remain Unanswered?

We were interested in identifying evidence comparing the long-term benefits and serious harms between combination therapy and intensification of statin monotherapy. Unfortunately, we identified only a few studies that reported mortality and serious adverse events with ezetimibe combined with statin as compared to higher potency statin monotherapy. These trials all lasted less than 12 weeks and very few events were reported. We found very limited evidence regarding these long-term benefits and serious harms among other combination therapy comparisons (bile acid sequestrants, fibrates, niacin, and omega-3 fatty acids). Overall, we are unable to conclude whether there are any long-term advantages or serious disadvantages to combination therapy with any agent as compared to intensification of statin monotherapy.

Few studies specifically evaluated high-risk subgroups of interest, which included patients with prior cardiovascular disease or patients with diabetes mellitus. Only comparisons of mid potency statin in combination with ezetimibe to high potency statin monotherapy had sufficient number of trials for evaluation. Among these trials, the strength of evidence is moderate in favor of combination therapy for lowering LDL-c as compared to statin monotherapy. Given that many providers may target these high-risk patients for LDL-c target< 70mg/dL per revised ATP III guidelines,[43] combination therapy with ezetimibe may help these patients achieve this goal. Future studies should consider comparing combination therapy (bile acid sequestrants, fibrates, niacin, omega-3 fatty acids) to intensification of statin monotherapy in these high-risk populations, as understanding what regimens result in better LDL-c lowering would inform providers on the best therapeutic options for these patients.

Very few studies included only elderly individuals (age>75), females, blacks, Asians or Hispanics. No studies included only Native Americans. Given the cardiovascular disease disparities identified among Black and Native American populations,[4] future studies should consider targeting these populations comparing combination therapy to intensification of statin monotherapy as these populations may be more likely to require an aggressive lipid-modifying regimen to achieve their LDL-c goals.

Findings in Relationship to what is Already Known

This report is an update of a 2009 AHRQ Effective Healthcare Program comparative effectiveness review. The prior review found a paucity of evidence to address these same key questions, and the authors concluded that there was insufficient evidence to determine whether any combination therapy held benefit over monotherapy.[59,60] We based this update on the prior review; however, a few key differences should be noted. We included only studies with patients of moderate or greater CHD risk who are clinically the most likely to require combination therapy or intensification of statin monotherapy to meet their ATP III lipid goals, while the prior review included all studies regardless of patient CHD risk. We also categorized statin combination therapy and monotherapy according to individual agents LDL-c lowering potency (low, mid, and high), while the prior review dichotomized agents into low-dose and high-dose. We also required there to be a difference in potency category between the combination therapy and monotherapy arms to reflect a real intensification of statin dose in the monotherapy as compared to the combination arm. These three differences influenced the populations that we included, as well as enabled us to standardize the comparisons of therapeutic regimens across different statin agents. As a result, we excluded many trials from this update that were included in the prior review.

We were able to make conclusions regarding several surrogate clinical markers. Many high profile clinical trials comparing combination therapy agents to statin monotherapy have shown that combination therapy can achieve better lipid outcomes. For example, ezetimibe + high potency simvastatin is more effective at lowering LDL-c than high potency simvastatin monotherapy (ENHANCE) and niacin + high potency simvastatin is more effective at raising HDL-c than high potency simvastatin monotherapy (AIM-HIGH).[49,52] These trials were not included in this review, as they did not meet our potency comparison requirements. In this review, we found moderate strength evidence supporting low potency statin in combination with either bile acid sequestrant or ezetimibe for lowering LDL-c as compared to mid potency statin monotherapy. There is also low strength evidence supporting mid potency statin in combination with ezetimibe for lowering LDL-c as compared to high potency statin monotherapy. Only the statin and ezetimibe combinations had HDL-c raising benefits, while there was no HDL-c difference with combination therapy with bile acid sequestrant. In contrast, there is moderate and low strength evidence supporting high potency statin monotherapy for lowering LDL-c as compared to mid potency statin in combination with fibrate and niacin, respectively. However, the combination of mid potency statin in combination with fibrate or niacin resulted in favorable HDL-c increases as compared to the high potency statin monotherapy.

In contrast to the prior review, we were also able to make some conclusions regarding harms of these therapeutic regimens. There is moderate strength evidence favoring high potency statin monotherapy in terms of lower rates of serious adverse effects as compared to mid potency statin in combination with ezetimibe. Combination therapy with ezetimibe has improved LDL-c and HDL-c outcomes, but may come at the potential cost of more serious adverse events for their patients.

Applicability

Many trials that met our inclusion criteria were implemented in populations of hyperlipidemic patients, and most were designed to evaluate effects on lipid measures and short-term harms. The results of most trials generalize to patients with hyperlipidemia uncomplicated by other major co-morbid conditions. Interestingly, we identified fewer trials that were conducted among high CHD risk patients such as those with diabetes or preexisting cardiovascular disease. These patients could benefit from improvement in their lipid profiles and are the most likely to be receiving more aggressive lipid-modifying regimens in clinical practice. We only identified adequate numbers of trials comparing mid potency statin in combination with ezetimibe to high potency statin monotherapy in these high-risk populations.

Interventions were similar across studies. It is important to note that many trials employed a medication titration regimen to specify how the doses of each medication should be increased to reach their target. This was especially common among trials with niacin, in order to minimize the medication side effects (flushing). These schedules may have improved the tolerability of the medications in the trial, and clinicians should be aware that a similar approach might need to be taken in clinical practice.

Most trials we identified were of relatively short duration, despite the fact that these medications are currently used in clinical practice as chronic, long-term medications. In addition, losses to followup and medication adherence by intervention arm were often not reported in trials, which may bias our results. While our findings may suggest that one therapeutic option provides a benefit over another, we cannot comment on the tolerability of or persistence to the regimen given the lack of data and short trial duration. Additional long-term trials are needed to compare the tolerability, side effects, and harms with prolonged use of these medications.

Implications for Clinical and Policy Decision-Making

These results may help aid individual decision-making and patient management. Overall, the findings suggest that healthcare providers should consider tailoring the lipid-modifying regimen based on individual patient needs. For example, a patient with low HDL-c and moderately increased LDL-c may benefit from mid potency statin in combination with fibrate or niacin rather than high potency statin monotherapy, as a patient would may be more likely to achieve both LDL-c and HDL-c goals with this regimen. For patients with low HDL-c and very elevated LDL-c, they may benefit from mid potency statin in combination with ezetimibe rather than high potency statin monotherapy. However, clinicians will need to weigh the greater likelihood of serious adverse events with this combination regimen when considering these options for their patients.

These results may also help provide an evidence base for future clinical practice guidelines and policy decisions. However, we suspect that the strength of evidence for most comparisons is too low to support guidelines or policy changes at this time.

Limitations of the Comparative Effectiveness Review Process

The strength of evidence was insufficient for many comparison outcome relationships, given a paucity of studies in these areas. We were only able to grade the strength of evidence for one outcome as high, despite numerous trials within some comparisons.

Trials were frequently downgraded during risk of bias assessment for lack of blinding by participant and study personnel (performance bias), for not reporting the blinding of outcome assessors (detection bias), or for not accounting for losses to followup or handling of incomplete data (attrition bias). In addition, some studies did not report an intention-to-treat analysis and others did not specify the number analyzed in each arm. All of these factors limited our ability to conduct meta-analyses. Substantial heterogeneity, clinical and statistical, precluded the presentation of summary estimates from most meta-analyses.

While we were able to standardize the potency of different doses of various statins, we were unable to classify the potency of the other lipid-modifying agents used in the combination therapy arms. We noted differential effects on lipid outcomes in some trials where the same potency statin was used in the combination arm, but different doses of the other agent were used.

Few studies reported variance estimates for the between group differences in any outcomes over time. In some instances, the studies did not report a mean difference or point estimate stating there was no significant difference between the groups..

Strengths and Limitations of the Evidence Base

Many studies included populations of at least moderate CHD risk for whom the decision between combination therapy and intensification of statin monotherapy is likely a clinical conundrum for both patients and healthcare providers. However, few trials specifically target those patients at highest CHD risk. Populations such as patients with diabetes or prior atherosclerotic cardiovascular disease represent a greater clinical challenge with respect to what their lipid treatment targets should be and how to accomplish these goals.

We excluded many studies because they did not compare combination therapy to intensification of statin monotherapy. Most trials that we excluded either compared a therapeutic regimen to placebo or compared combination and monotherapy arms of the same statin potency. Neither of these study designs enables us to answer the questions in this update review.

Many studies either did not evaluate or were of insufficient duration to adequately assess long-term clinical outcomes including mortality, acute coronary events, and revascularization procedures. Studies often pooled results on adverse effects across arms, which limited our ability to determine whether different doses and potencies of combination and monotherapy led to different rates of these events. Ultimately, clinicians hope to reduce the likelihood of negative clinical events for their patients by achieving their lipid goals with medications while minimizing the risk for side effects and harms. Providing evidence that compares combination therapy and intensification of statin monotherapy with respect to these important clinical outcomes and harms would aid decision-making for clinicians and highlight for patients the health benefits of adhering to these regimens.

Finally, this report focuses primarily on LDL-c and HDL-c outcomes. While many trials focused on examining these outcomes, the clinical field may be moving towards emphasizing additional lipid measures such as non-HDL-c and ApoB as new targets. These other lipid measures were not included as a part of our outcomes, except for non-HDL-c among patients with diabetes. We did not include these measures at this time given the controversy and uncertainty of what the new ATP IV goals may be. If these measure do in fact become a part of ATP IV recommendations, then it would be appropriate to include these measures as outcomes for all patient populations in future systematic reviews. In addition, the ADA and ACCF have released guidelines that suggests a new LDL-c goal <70 mg/dL for the highest risk patients, rather than a goal of <100 mg/dL in ATP III.[46] In this report, we included studies that defined achieving ATP III LDL goal as <100 mg/dL for the highest risk patients. However, if the upcoming release of ATP IV makes similar recommendations to ADA and ACCF, then this report would include ineligible comparisons of the effectiveness of combination therapy regimens to intensification of statin monotherapy in attaining LDL goals for these highest risk patients.

Future Research Needs

We suggest that most comparisons and outcomes that have low or insufficient evidence are future research needs. In order to answer whether there are long-term benefits with respect to mortality, acute coronary events, and revascularization procedures, future investigators need to make these endpoints the primary outcomes of their trials and ensure that trials are of sufficient duration to actually capture these events (at least 12 months or preferably longer). Recent trials such as ENHANCE, ACCORD, and AIM-HIGH have failed to show any additional clinical benefit of combination therapy as compared to statin monotherapy.[49,52,54] While the forthcoming IMPROVE-IT trial may be able to clarify whether ezetimibe + simvastatin is superior to simvastatin alone with respect to cardiovascular deaths, MI or strokes, this trial uses equivalent doses of simvastatin in the combination and monotherapy arms.[53] This trial will not provide information to make decisions about the effectiveness of intensification of statin monotherapy compared to combination therapy. Therefore, additional trials to answer this specific question that are of sufficient duration to capture these outcomes are needed. Trials of longer duration would also better reflect how these medications are currently used in clinical practice, where they are considered chronic use medications. These trials would be able to evaluate outcomes relevant to medication persistence such as tolerability, side effects, and serious adverse events.

We further suggest that future studies focus on high-risk CHD populations and populations with greater burden of cardiovascular disease to determine which strategy provides better short-term improvements in lipid profile and long-term clinical benefits. These populations would include patients with diabetes and preexisting cardiovascular disease, as well as Black and Native American populations.[4] It may be worthwhile to explore differences between men and women, as the ACCORD trial showed benefit of combination therapy with fibrate in men and potential harms with this combination therapy in women.[54] These studies would have tremendous impact on clinical practice, as these patients are the most likely to need a more aggressive lipid-modifying regimen.

While the current head-to-head comparisons of a combination regimen to intensification of statin therapy may not answer important clinical questions, these trials can not help clinicians decide between different combination therapy options. The next step to inform clinical decisionmaking would be to help clinicians in selecting the most appropriate lipid-modifying regimen from all available options. We suggest that future studies conduct head-to-head comparisons of multiple combination regimens against each other as well as intensification of statin monotherapy to address this need.

A number of trials have shown that non-statin lipid modifying medications may not improve or even potentially worsen some clinical outcomes. Future studies may need to consider including non-statin monotherapy as another comparison group with respect to clinical outcomes and harms. Such information would be informative to clinicians who may be considering non-statin monotherapy as a treatment option.

There are design and reporting considerations that should be considered for future studies. Intervention trials should be of sufficient duration to assess the efficacy of interventions on long-term clinical outcomes like mortality, acute coronary events, and revascularization procedures. We suggest that one-year should be a minimum duration of followup for these interventions. We would also encourage future studies to report variance estimates for all outcomes, as well as account for losses to followup by arm and report the number analyzed in each arm. Finally, we would also encourage studies to report adverse event outcomes by individual arm, rather than reporting only pooled results. Different doses and potencies of therapeutic regimens result in differential side effects and harms and this would be important to capture.

Conclusions

In general, combination of statin with ezetimibe or bile acid sequestrant lowered LDL-c better than intensification of statin monotherapy, while intensification of statin monotherapy was preferable in reducing LDL-c when considering combination therapy of statin with niacin or fibrate. Combination of statin with ezetimibe, niacin, or fibrate raised HDL-c better than intensification of statin monotherapy. Additional studies need to evaluate long-term clinical benefits and factors that influence medication persistence such as tolerability and harms, which would provide important information for clinical decision-making, patient choice, and clinical practice guidelines.

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